# CLINICAL STUDY PROTOCOL

## A Phase 1b Dose-Escalation Study of Cabozantinib (XL184) Administered Alone or in Combination with Atezolizumab to Subjects with Locally Advanced or Metastatic Solid Tumors

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| **PROTOCOL NUMBER:** | XL184-021 | |
| **STUDY TREATMENT:** | Cabozantinib (XL184) and Atezolizumab | |
| **IND NUMBER:** | 72,596 | |
| **EudraCT NUMBER:** | 2017-001792-24 | |
| **SPONSOR:** | Exelixis, Inc.<br>1851 Harbor Bay Parkway<br>Alameda, CA 94502 | |
| **MEDICAL MONITOR:** | Dominic Curran, MBChB | |
| **FINAL DATE:** | 24 March 2017 | |
| **DATE AMENDED:** | 20 December 2017 | **PROTOCOL AMENDMENT: 1.0** |
| **DATE AMENDED:** | 31 August 2018 | **PROTOCOL AMENDMENT: 2.0** |
| **DATE AMENDED:** | 22 February 2019 | **PROTOCOL AMENDMENT: 3.0** |
| **DATE AMENDED:** | 02 July 2019 | **PROTOCOL AMENDMENT: 4.0** |
| **DATE AMENDED:** | 15 November 2019 | **PROTOCOL AMENDMENT: 5.0** |
| **DATE AMENDED:** | 16 April 2020 | **PROTOCOL AMENDMENT: 6.0** |

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## PROTOCOL APPROVAL PAGE

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Approval of protocol by sponsor:

16-APR-20

Dominic Curran, MBChB — Date
Senior Medical Director, Clinical Development

16 April 2020

Gisela Schwab, MD — Date
President Product Development and Medical Affairs & Chief Medical Officer

## 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

# SYNOPSIS

**TITLE**

A Phase 1b Dose-Escalation Study of Cabozantinib (XL184) Administered Alone or in Combination with Atezolizumab in Subjects with Locally Advanced or Metastatic Solid Tumors

**PROTOCOL NUMBER**

XL184-021

**CLINICAL PHASE**

Phase 1b

**RATIONALE**

Multi-targeted tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs) represent two systemic modalities that have been instrumental in the recent advancements of anticancer treatment over the past several years. Both classes of therapies have demonstrated broad clinical effects leading to new approved treatment options across multiple tumor types. The success of these therapy types as single agents with distinct mechanisms of action has naturally led to interest in evaluating combinations of TKIs with ICIs in search of further, possibly synergistic, anticancer clinical effects.

Atezolizumab is a humanized immunoglobulin (Ig) G1 monoclonal antibody that targets programmed death receptor 1 ligand (PD-L1) and inhibits the interaction between PD-L1 and its receptors, programmed death receptor 1 (PD-1) and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Atezolizumab injection for intravenous (IV) use (1200 mg once every 3 weeks [q3w]) has been approved in the US and 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 the 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 prescribing information [US PI] and European Medicines Agency Summary of Product Characteristics [EMA SmPC]). Recently, atezolizumab was also granted accelerated approval in the US for treatment in combination with paclitaxel protein-bound (nab-paclitaxel) for adult patients with unresectable locally advanced or metastatic triple negative breast cancer (TNBC) whose tumors express PD-L1 (Schmid et al 2018) and was also approved for first-line treatment in combination with carboplatin and etoposide in adult patients with extensive-stage small cell lung cancer (ES-SCLC; Horn et al 2018, Tecentriq US PI). Treatment with atezolizumab is generally well-tolerated but can be associated with immune-related adverse events (irAEs).

Further, atezolizumab has demonstrated encouraging clinical activity in other tumor treatment settings: monotherapy in treatment-naïve advanced-stage NSCLC (Peters et al 2017), combination with chemotherapy and bevacizumab in treatment-naive advanced-stage NSCLC (Sociniski et al 2018), monotherapy in advanced renal cell carcinoma (RCC) (McDermott et al 2016), monotherapy in metastatic castration-resistant prostate cancer (mCRPC; Kim et al 2018), combination with bevacizumab in treatment-naïve advanced RCC (Motzer et al 2018), monotherapy in advanced triple-negative breast cancer (TNBC; Schmid et al 2017), monotherapy in advanced ovarian cancer (OC; Infante et al 2016), monotherapy in advanced endometrial cancer (EC; Fleming et al 2017), monotherapy and

combination with bevacizumab in treatment-naïve hepatocellular carcinoma (HCC; Stein et al 2018; Roche data on file), monotherapy in advanced gastric cancer (GC; Taieb et al 2018), combination with bevacizumab (± chemotherapy) in advanced colorectal cancer (CRC; Hochster et al 2017), and monotherapy in advanced head and neck (H & N) cancer (Bahleda et al 2017). In addition, atezolizumab is currently being evaluated in combination with bevacizumab or molecular targeted therapies in anaplastic and differentiated thyroid cancer (NCT03181100).

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

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

Cabozantinib has also demonstrated encouraging clinical activity in other tumor indications: monotherapy in advanced urothelial carcinoma (Apolo et al [J Clin Oncol] 2016), in combination with ICIs in advanced urothelial carcinoma (Nadal et al 2018, Nadal et al 2017, Apolo et al [Ann Oncol] 2016), monotherapy in CRPC (Smith et al 2013, Smith et al 2014, Basch et al 2015), monotherapy or in combination with erlotinib in advanced NSCLC (Schöffski et al 2017, Neal et al 2016), monotherapy in RET-rearranged NSCLC (Drilon et al 2016), monotherapy in advanced TNBC (Tolaney et al 2017), monotherapy in advanced OC (Matulonis et al 2016, Vergote et al 2017), monotherapy in advanced EC (Dhani et al 2017; Mandilaras et al 2017), monotherapy in advanced GC (Schöffski et al 2017), in combination with panitumumab in CRC (Strickler et al 2016), and monotherapy in radioactive-iodine refractory DTC (Brose et al 2018, Cabanillas et al 2014, Cabanillas et al 2017).

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

In this Phase 1b study, a total of 12 subjects with advanced RCC were enrolled in the Dose-Escalation Stage using a 3 + 3 design. Six (6) subjects were evaluated at both the 40-mg and 60-mg cabozantinib dose levels in combination with the standard dose of atezolizumab. Both dose levels of cabozantinib were generally well tolerated, and no dose-limiting toxicities (DLTs) were observed. 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 for the Expansion Cohorts.

The Expansion Stage is evaluating the efficacy and safety of cabozantinib 40 mg qd in combination with atezolizumab 1200 mg q3w across 20 tumor-specific cohorts of the following tumor types: RCC, UC, CRPC, NSCLC, triple negative breast cancer (TNBC), ovarian cancer (OC), endometrial cancer (EC), hepatocellular cancer (HCC), gastric cancer/gastroesophageal junction cancer/lower esophageal cancer (GC/GEJC/LEC), colorectal cancer (CRC), H&N cancer, and differentiated thyroid cancer (DTC). In order to establish the individual contributions of the components of the combination therapy, the Expansion Stage also includes three exploratory single-agent cabozantinib cohorts (UC, CRPC, and NSCLC) and one single-agent atezolizumab cohort (CRPC). The Study Oversight Committee (SOC) will review the efficacy and safety of the initially enrolled subjects (approximately 30 subjects in each cohort) and may recommend enrollment extension for up to 10 cohorts in which encouraging clinical activity has been demonstrated. The SOC can also recommend additional enrollment at a higher dose of cabozantinib (60 mg qd orally) in combination with 1200 mg atezolizumab q3w IV for tumor cohorts with modest clinical activity at cabozantinib 40 mg in combination with atezolizumab. The single-agent atezolizumab cohort will initially enroll 10 subjects. Enrollment with approximately 30 subjects will depend on the observed efficacy among the first 10 enrolled subjects. The Expansion Stage was initiated on 26 March 2018. At the time of this protocol amendment the SOC has recommended extended enrollment for Cohort 1 (clear cell RCC), Cohort 6 (CRPC), and Cohort 7 (NSCLC, prior ICI therapy) following review of efficacy and safety data of the initially enrolled subjects.

This amendment provides for subjects enrolling in the cohorts receiving single-agent treatment with either cabozantinib or atezolizumab the opportunity to receive combination treatment with cabozantinib and atezolizumab after Investigator-assessed radiographic disease progression per Response Evaluation Criteria in Solid Tumors (version 1.1) (RECIST 1.1) given these subjects meet the eligibility criteria for receiving combination treatment (Second Agent Add-On Stage).

XL184-021 Protocol Amendment 6.0 introduced considerations and study-related measures necessary due to the COVID-19 pandemic.

**OBJECTIVES**

Dose-Escalation Stage (Combination Therapy Cohorts):

The primary objective is as follows:

- To determine the maximum tolerated dose (MTD) and/or recommended dose and schedule for the subsequent Expansion Stage of daily oral administration of cabozantinib in subjects with solid tumors when taken in combination with atezolizumab.

The secondary objective is as follows:

- To evaluate the plasma pharmacokinetics (PK) of daily oral administration of cabozantinib in subjects with solid tumors when given in combination with atezolizumab.
- To assess safety of the combination therapy through the evaluation of incidence and severity of nonserious adverse events (AEs) and serious adverse events (SAEs), including immune-related adverse events (irAEs) and adverse events of special interest (AESIs).

The exploratory objective is as follows:

- Correlation of immune cell, tumor cell, and blood biomarker analyses with clinical outcome
- ORR as assessed by the Investigator per RECIST 1.1

Expansion Stage (Combination-Therapy Cohorts):

The primary objective and endpoint is as follows:

- To evaluate preliminary efficacy of the combination therapy by estimating the ORR as assessed by the Investigator per RECIST 1.1

The secondary objective is as follows:

- To assess safety for the combination therapy through the evaluation of incidence and severity of nonserious AEs and SAEs, including irAEs and AESIs.

The exploratory objectives and endpoints are as follows:

- ORR as assessed by the Investigator per immune-related RECIST (irRECIST) for immune response
- Duration of response (DOR) as assessed by the Investigator per RECIST 1.1
- Progression-free survival (PFS) as assessed by the Investigator per RECIST 1.1
- ORR, DOR, and PFS as assessed by a Blinded Independent Radiology Committee (BIRC) per RECIST 1.1 for selected cohorts
- Overall survival (OS)
- Correlation of immune cell, tumor cell, and blood biomarker analyses with clinical outcome
- Changes in tumor infiltration and/or histology or other molecular changes as determined from optional tumor biopsy
- To further evaluate the plasma pharmacokinetics (PK) of daily oral administration of cabozantinib in subjects with solid tumors when given in combination with atezolizumab
- Tumor marker changes from baseline in select tumor indications
- Evaluation of mismatch repair (MMR) and microsatellite instability (MSI) status in relevant tumor indications
- Changes in prostate-specific antigen (PSA) from baseline for CRPC cohorts

Exploratory Single-Agent Cabozantinib (SAC) Cohorts:

- Descriptive efficacy, safety, PK, and biomarker analyses of single-agent cabozantinib (SAC) in UC, CRPC, and NSCLC subjects
- Descriptive efficacy and safety analyses of combination therapy after progression on single-agent cabozantinib therapy

Exploratory Single-Agent Atezolizumab (SAA) Cohort:

- Descriptive efficacy, safety, PK, and biomarker analyses of single-agent atezolizumab (SAA) in CRPC subjects
- Descriptive efficacy and safety analyses of combination therapy after progression on single-agent atezolizumab therapy

## STUDY DESIGN

This is a multicenter, open-label Phase 1b study to assess safety, tolerability, preliminary efficacy, and PK of cabozantinib alone or taken in combination with atezolizumab in subjects with advanced cancer.

The combination of cabozantinib with atezolizumab will be evaluated first in a Dose-Escalation Stage and subsequently in an Expansion Stage. The Dose-Escalation Stage allows enrollment of subjects with advanced RCC and UC using different dose levels of cabozantinib and a standard dose level of atezolizumab. The Expansion Stage allows enrollment in 20 different tumor cohorts including subjects with advanced RCC, UC, CRPC, NSCLC, TNBC, OC, EC, HCC, GC/GEJC/LEC, CRC, H&N cancer, and DTC to receive the recommended dose of the combination therapy from the Dose-Escalation Stage. In addition, the Expansion Stage includes three single-agent cabozantinib (60 mg) cohorts in UC, CRPC, and NSCLC as well as one single-agent atezolizumab (1200 mg) cohort in CRPC, which will evaluate the individual contributions of the components of the combination therapy.

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

1. **Dose-Escalation Stage**: to determine the schedule and MTD and/or recommended Expansion Stage dose of cabozantinib when taken in combination with a standard dosing regimen of atezolizumab (1200 mg infusion, once every 3 weeks). Three cabozantinib tablet daily dose levels will be considered for evaluation: 20 mg, 40 mg, and 60 mg. Subjects will accrue in escalation cohorts of 3-6 subjects using a "3 plus 3" design and dosing will begin at the 40 mg dose level of cabozantinib. Subjects with either advanced UC or RCC will be eligible for these Dose Escalation cohorts, and cohorts may comprise mixtures of subjects with those tumor types. During this stage the decision to open a new cohort will be made by the Cohort Review Committee when all subjects in the current cohort have been followed for at least 21 days following first dose of atezolizumab (defined as the DLT Evaluation Period). All available safety and PK data will be considered in a decision to dose escalate or de-escalate the next cohort or to expand the current cohort. An MTD of cabozantinib will be defined as the highest evaluated dose level at which not more than 1 out of 6 subjects experiences a DLT. The recommended dose and schedule for the Expansion Stage will be determined by the Cohort Review Committee based on DLTs and other relevant safety information.

| Relative Dose Level | Cabozantinib | Atezolizumab |
|---|---|---|
| 2 | 60 mg oral qd | 1200 mg IV q3w |
| 1 | 40 mg oral qd | 1200 mg IV q3w |
| -1 | 20 mg oral qd | 1200 mg IV q3w |

IV, intravenous; qd, once daily; q3w, once every three weeks

Dose-limiting toxicity will be determined by the Cohort Review Committee upon review of all available data and is defined as any of the following occurring during the DLT Evaluation Period:

1. Any related AE that in the opinion of the Cohort Review Committee is of potential clinical significance such that further dose escalation of cabozantinib would expose subjects to unacceptable risk.
2. Any related ≥ Grade 3 AE which is unexpected in severity and/or duration compared with the known safety profiles of cabozantinib and atezolizumab when used as single agents, and that cannot be managed by dose modification (reduction or interruption) and adequate supportive care, and requires permanent discontinuation of cabozantinib and/or atezolizumab.

3. Inability to take ≥ 75% of the total planned cabozantinib dose for the DLT Evaluation Period because of a treatment-related AE leading to dose reductions and/or interruptions

The initial study design included two possible dosing schedules: the Standard Dosing Schedule or the Cabozantinib Run-In Dosing Schedule. The Dose-Escalation Stage was initiated with the Standard Dosing Schedule. The Cabozantinib Run-In Dosing Schedule could have been implemented upon request of the Cohort Review Committee if no recommended Expansion Stage dose had been identified after the evaluation of the Standard Dosing Schedule.

Standard Dosing Schedule: Initial dose escalation cohorts will receive the combination regimen on a "Standard Dosing Schedule" with the first infusion of atezolizumab given on the same day as the first dose of cabozantinib (on Cycle 1 Day 1 [C1D1]).

Cabozantinib Run-In Dosing Schedule: If review of safety data for all enrolled subjects who received the Standard Dosing Schedule did not yield a recommended dose for the Expansion Stage, the Cohort Review Committee could have decided to enroll additional cohorts treated on a "Cabozantinib Run-In Dosing Schedule." Subjects in these cohorts would have received the first infusion of atezolizumab on C2D1, 21 days after their first dose of single-agent cabozantinib (same possible dose levels as described above). The subjects would have only been evaluated for DLTs during the 21-day period after receiving the first infusion of atezolizumab (the DLT Evaluation Period). The purpose of this dosing schedule would have been to help the Cohort Review Committee assess whether subjects would have improved tolerability to the combination of cabozantinib and atezolizumab if first given the opportunity to optimize their tolerability to cabozantinib alone during a three week run-in period.

Prior to Protocol Amendment 2.0 the recommended dose for the Expansion Stage had already been identified using the Standard Dosing Schedule. The Cabozantinib Run-In Dosing Schedule will therefore not be implemented in this study.

2. **Expansion Stage**: to further assess the efficacy, safety, PK, and pharmacodynamics of cabozantinib in combination with atezolizumab in multiple different tumor types using the recommended dose and schedule as determined by the Cohort Review Committee in the Dose-Escalation Stage. In addition, single-agent cohorts will enroll subjects to receive either cabozantinib only or atezolizumab only to evaluate the individual contributions of the components of the combination therapy.

   After initial enrollment of approximately 30 subjects, cohorts in the Expansion Stage, except the SAA Cohort, may extend enrollment (see Figure 1) based on the available clinical data per the SOC. The extended enrollment will be limited to up to 10 cohorts in the Expansion Stage with a maximum enrollment of 1000 additional subjects. Extended enrollment beyond 30 subjects is not allowed for the SAA Cohort. The SAC Cohorts and the SAA Cohort will open to enrollment at the discretion of the Sponsor. The Sponsor can decide to stop enrollment of any cohort at any time (eg, due to slow subject accrual).

   ***Combination-Therapy Expansion Cohorts:***

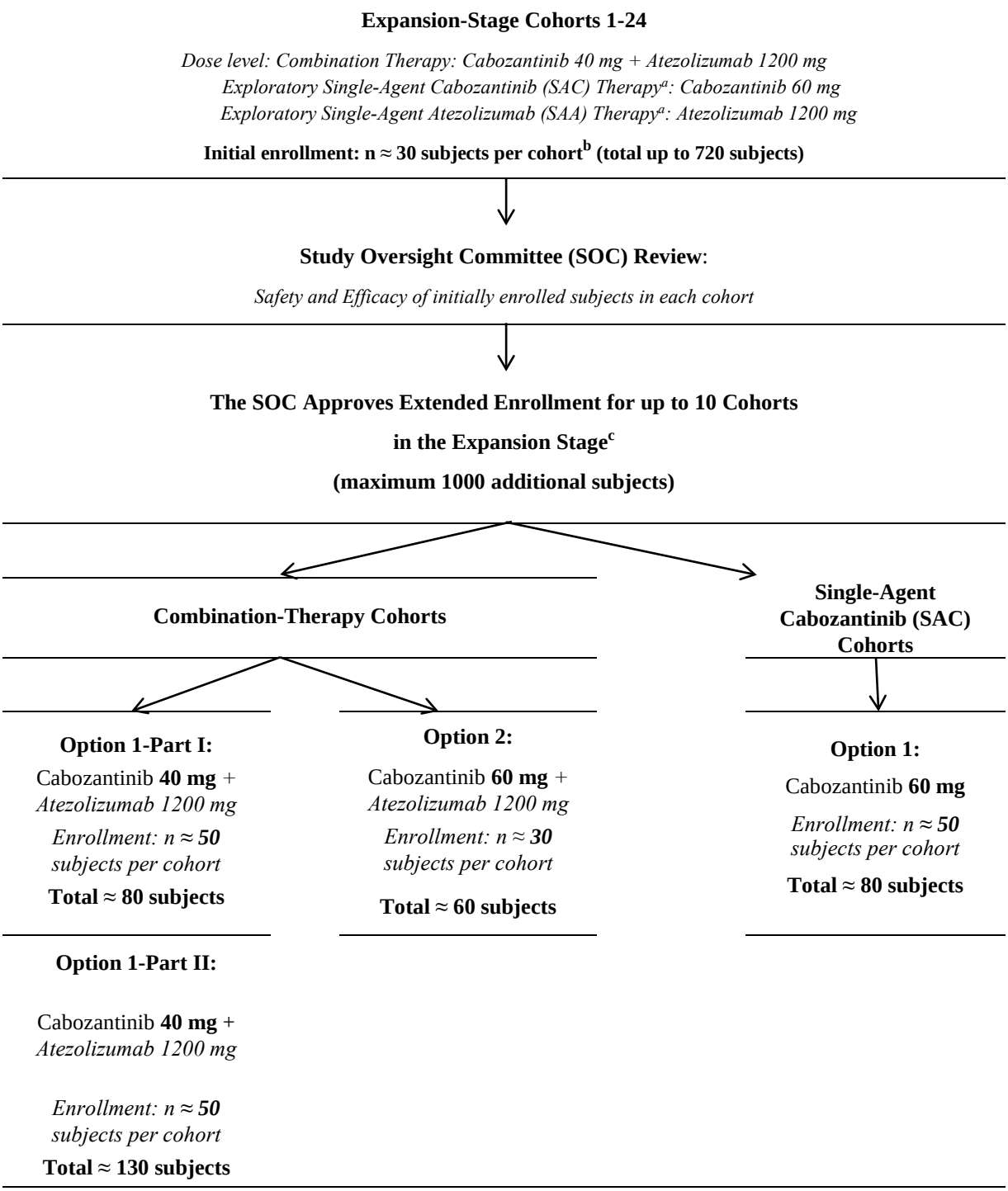
   All Combination-Therapy Expansion Cohorts will initially enroll approximately 30 subjects with cabozantinib 40 mg in combination with atezolizumab 1200 mg as the assigned starting dose (see Table 1 for a summary of Expansion Cohorts 1-18 and 23-24).

   Because of the high unmet medical need of patients with advanced, incurable cancer, the SOC may decide after periodic review of safety and efficacy data of approximately 30 subjects of an Expansion Cohort to allow for additional enrollment to further assess the clinical activity and safety of the combination therapy. Extended

enrollment of a Combination-Therapy Expansion Cohort will be implemented based on only one of the following two Extended Enrollment Options (see Figure 1 below):

- Extended Enrollment Option 1:
  - Part I: Combination-Therapy Expansion Cohorts may enroll up to approximately 50 additional subjects to receive the same dosing regimen as the initially enrolled approximately 30 subjects (cabozantinib 40 mg + atezolizumab 1200 mg) upon approval by the SOC. Decisions by the SOC regarding additional enrollment will be based on the clinical significance of the achieved ORR in the Expansion Cohorts and will include an evaluation of the lower bound of confidence intervals for ORR in the initially enrolled subjects. A minimum observed ORR of around 20% or more will be used as a target (though not a requirement) for the SOC to consider Part I of Extended Enrollment Option 1 (Section 9.1.2). The magnitude of ORR deemed clinically meaningful by the SOC may vary by cohort. The committee may also consider other factors of clinical benefit (eg, time to response, duration of response, safety/tolerability) in the decision to extend enrollment.
  - Part II: Combination-Therapy Expansion Cohorts may further enroll up to approximately 50 additional subjects for a maximum total of approximately 130 subjects in an expansion cohort. These subjects will receive the same dosing regimen as the previously enrolled subjects (cabozantinib 40 mg + atezolizumab 1200 mg) upon approval by the SOC. Decisions by the SOC regarding further extended enrollment in Part II of Extended Enrollment Option 1 will be based on the clinical significance of the achieved ORR in the Expansion Cohorts and will include an evaluation of the lower bound of confidence intervals for ORR in the previously enrolled subjects. A minimum observed ORR of around 35% or more will be used as a target (though not a requirement) for the SOC to consider Part II of the Extended Enrollment Option 1 (Section 9.1.2). Part II extension will only apply to tumor indications with a high-unmet medical need and very encouraging efficacy and safety data observed in Part I.
- Extended Enrollment Option 2: For Combination-Therapy Expansion Cohorts in which the initially enrolled approximately 30 subjects do not meet the criteria for Extended Enrollment Option 1, the SOC may decide to allow each selected Expansion Cohort to enroll up to approximately 30 additional subjects to receive the highest dose level of cabozantinib explored in the Dose-Escalation Stage (60 mg) in combination with atezolizumab 1200 mg to explore whether the higher cabozantinib dose will lead to improved clinical activity and maintain an acceptable safety profile.

**Figure 1: Expansion Stage Enrollment Overview (Maximum 1720 Subjects)**




[a] Subjects who radiographically progress (per Investigator per RECIST 1.1) on single-agent treatment in the SAC or SAA Cohorts may be able to receive combination treatment with cabozantinib and atezolizumab in the Second Agent Add-On Stage if they are deemed eligible (see Section 3.5.2.4). These subjects will receive atezolizumab doses of 1200 mg IV q3w and cabozantinib doses at the lower of 40 mg PO qd or their most recently received dose level.

[b] In the SAA Cohort, an initial evaluation of clinical activity will be performed in the first 10 subjects prior to further enrollment in this cohort. Maximum enrollment of the SAA Cohort will be 30 subjects.

[c] Extended enrollment is not allowed for SAA Cohort 22. Refer to Section 3.5.2.3 for subject enrollment in SAA Cohort 22.

***Exploratory Single-Agent Cabozantinib (SAC) Cohorts**:*

Three SAC Cohorts will each initially enroll approximately 30 subjects with advanced UC, CRPC, or NSCLC (see Table 1 for a summary of SAC Cohorts). Subjects in the SAC Cohorts will receive single-agent cabozantinib 60 mg qd. The SOC may decide whether more subjects are needed to identify the contribution of cabozantinib to the combination treatment based on the results from the matching combination therapy cohorts. Each of these cohorts will be allowed to enroll up to approximately 50 additional subjects at the same dosing regimen of cabozantinib as the initially enrolled subjects. The SAC Cohorts will open for enrollment at the discretion of the Sponsor. The Sponsor can decide to stop enrollment in the SAC cohorts at any time (eg, due to slow subject accrual). Subjects enrolled in the SAC cohorts with documented Investigator-assessed radiographic progression per RECIST 1.1 following treatment with single-agent cabozantinib may be eligible to receive the combination therapy (Second Agent Add-On Stage). These subjects will receive atezolizumab doses of 1200 mg IV q3w and cabozantinib doses at the lower of 40 mg by mouth (PO) qd or their most recently received dose level. Please see Section 3.5.2.4 for details.

***Exploratory Single-Agent Atezolizumab (SAA) Cohort**:*

One SAA Cohort will initially enroll 10 subjects with advanced CRPC (see Table 1) since there are limited data available on the clinical activity of atezolizumab in previously treated mCRPC (Kim et al 2018). Additional enrollment will be conditional upon responses observed among the first 10 enrolled subjects. If there are at least two confirmed responses (PR or CR) per RECIST 1.1 among the first 10 subjects enrolled, up to 20 additional subjects may be enrolled for a maximum total of 30 subjects in this cohort. Subjects in this cohort will receive the standard dosing regimen of atezolizumab (1200 mg IV, q3w). Extended enrollment beyond 30 subjects is not allowed in this cohort. The SAA Cohort will open for enrollment at the discretion of the Sponsor. The Sponsor can decide to stop enrollment of this cohort at any time (eg, due to slow subject accrual). Subjects enrolled in the SAA cohort who exhibit Investigator-assessed radiographic progression per RECIST 1.1 following treatment with single-agent atezolizumab may be eligible to receive the combination therapy. Subjects will receive atezolizumab doses of 1200 mg IV q3w and cabozantinib doses of 40 mg PO qd. Please see Section 3.5.2.4 for details.

All subjects enrolled in the Expansion Stage will be following the same frequency of assessments with the exception of the DTC Cohort (Expansion Cohort 18) which follows a different tumor imaging schedule. For more details regarding the eligibility of subjects for this study refer to inclusion and exclusion criteria. Rationales for enrollment in each Expansion-Stage Cohort are provided in Section 1.3.1.

**Table 1: Summary of All Combination-Therapy and Single-Agent Cohorts in the Expansion Stage**

| Cohort | Tumor Type (Histology) | Abbreviated Eligibility Description | Initial Cohort Size (n) |
|---|---|---|---|
| ***Combination-Therapy Cohorts*** | | | |
| 1 | RCC (clear cell) | No prior systemic anticancer therapy | 30 |
| 2 | UC (transitional cell) | Prior platinum-containing chemotherapy | 30 |
| 3 | UC (transitional cell) | Cisplatin-ineligible but no prior systemic anticancer therapy | 30 |
| 4 | UC (transitional cell) | Cisplatin-eligible but no prior systemic anticancer therapy | 30 |
| 5 | UC (transitional cell) | Prior immune checkpoint inhibitor therapy | 30 |
| 6 | CRPC (adeno) | Prior enzalutamide and/or abiraterone therapy | 30 |
| 7 | NSCLC (non-squamous) | Prior immune checkpoint inhibitor therapy | 30 |
| 8 | NSCLC (non-squamous) | No prior immune checkpoint inhibitor therapy | 30 |
| 9 | NSCLC (EGFR mutant, non-squamous) | Prior EGFR-targeting TKI therapy (prior immune checkpoint inhibitor therapy allowed if given in combination with chemotherapy) | 30 |
| 10 | RCC (non-clear cell) | Treatment naïve or prior systemic anticancer therapy | 30 |
| 11 | TNBC[a] (adeno) | Prior systemic anticancer therapy (prior immune checkpoint inhibitor therapy allowed) | 30 |
| 12 | OC[b] (epithelial) | Platinum-resistant or refractory | 30 |
| 13 | EC (serous or endometrioid) | Prior systemic anticancer therapy | 30 |
| 14 | HCC (adeno) | No prior systemic anticancer therapy | 30 |
| 15 | GC/GEJC/LEC (adeno) | Prior platinum- or fluoropyridine-containing therapy | 30 |
| 16 | CRC (adeno) | Prior fluoropyrimidine therapy with oxaliplatin or irinotecan | 30 |
| 17 | H&N (squamous) | Prior platinum-containing chemotherapy (prior immune checkpoint inhibitor therapy allowed) | 30 |
| 18 | DTC (follicular, papillary, and poorly differentiated) | No prior systemic anticancer therapy for radioiodine (RAI)-refractory disease | 30 |
| 23 | CRPC (adeno, high risk) | Prior enzalutamide or abiraterone therapy (no prior docetaxel initiated for mCRPC) | 30 |
| 24 | CRPC (adeno, high risk, prior chemo) | Prior enzalutamide and/or abiraterone therapy and prior taxane-based chemotherapy initiated for mCRPC | 30 |
| ***Exploratory Single-Agent Cabozantinib (SAC) Cohorts[c,d]*** | | | |
| 19 | UC (transitional cell) | Prior immune checkpoint inhibitor therapy | 30[c] |
| 20 | NSCLC (non-squamous) | Prior immune checkpoint inhibitor therapy | 30[c] |
| 21 | CRPC (adeno, high risk) | Prior enzalutamide or abiraterone therapy (no prior docetaxel initiated for mCRPC) | 30[c] |
| ***Exploratory Single-Agent Atezolizumab (SAA) Cohort[d,e]*** | | | |
| 22 | CRPC (adeno, high risk) | Prior enzalutamide or abiraterone therapy (no prior docetaxel initiated for mCRPC) | 30[e] |
| | | **Total initial enrollment** | **720[f]** |

Adeno, adenocarcinoma; CRC, colorectal cancer; CRPC, castration-resistant prostate cancer; DTC, differentiated thyroid cancer; EC, endometrial cancer; EGFR, epidermal growth factor; GC/GEJC/LEC, gastric cancer, gastro-esophageal junction cancer, and lower esophageal cancer; H&N, head and neck cancer; HCC, hepatocellular cancer; HER-2, hormone epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer; OC, ovarian cancer; RCC, renal cell cancer; SAA, single-agent atezolizumab; SAC, single-agent cabozantinib; TKI, tyrosine kinase inhibitor; TNBC, triple-negative breast cancer; UC, urothelial cancer.

[a] Subjects' tumor samples must have tested negative for HER-2/neu, estrogen receptors, and progesterone receptors.

[b] The ovarian cancer cohort may also include subjects with primary peritoneal cancer and fallopian tube cancer.

[c] Exploratory SAC Cohorts may extend enrollment with up to approximately 50 additional subjects beyond the initially enrolled approximately 30 subjects per cohort per the SOC.

[d] Subjects in the SAC and SAA cohorts who radiographically progress (per Investigator per RECIST 1.1) on single-agent therapy will have the opportunity to receive combination treatment with cabozantinib and atezolizumab if they meet eligibility requirements in the Second Agent Add-On Stage (see Section 3.5.2.4)

[e] Exploratory SAA Cohort will initially enroll 10 subjects and may enroll up to 20 additional subjects for a maximum total of 30 subjects based upon the initial response among the first 10 enrolled subjects (see Section 3.5.2.3). Enrollment beyond 30 subjects is not allowed in this cohort.

[f] Approximately 30 subjects may be initially enrolled into each of the Combination-Therapy Expansion Cohorts and SAC Cohorts. Up to 10 cohorts in the Expansion Stage except the SAA Cohort (see footnote **e** above) may enroll up to an additional approximately 100 subjects each in the Combination-Therapy Cohorts and/or up to an additional approximately 50 subjects each in the SAC Cohorts.

In the Expansion Stage, Cohorts 5 and 19 (UC) have identical eligibility criteria, as do Cohorts 7 and 20 (NSCLC) and Cohorts 21-23 (high-risk CRPC). Assignment of UC subjects to either Cohort 5 or 19, NSCLC subjects to either Cohort 7 or 20, and high-risk CRPC subjects to Cohort 21, 22, or 23 will be done by the Sponsor or designee. Subjects will be randomized into the cohorts open to enrollment following the eligibility review process by the Sponsor. Randomized cohort assignment will be implemented as long as two or more cohorts with identical eligibility criteria are open to enrollment. Refer to Section 3.5.2 for cohort enrollment details.

**Treatment Periods:**

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

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

Treatment Period: Eligible subjects will receive open-label cabozantinib (20, 40, or 60 mg orally administered qd). The date of the first dose of cabozantinib will be defined to be C1D1. Atezolizumab (1200 mg infusion) will be administered once every three weeks (-2 days) on Day 1 of each cycle starting on C1D1 for subjects in combination therapy cohorts and the SAA Cohort.

Permitted study drug modifications to manage AEs comprise dose reductions (from 60 mg to 40 mg qd, from 40 mg to 20 mg qd, or from 20 mg qd to 20 mg every other day [qod]) or interruptions for cabozantinib and dose delays for atezolizumab.

Subjects will receive study treatment as long as they continue to experience clinical benefit in the opinion of the investigator or until there is unacceptable toxicity, the need for subsequent systemic anticancer treatment, or until any other reasons for treatment discontinuation listed in the protocol. Treatment may continue after radiographic progression as long as the Investigator believes that the subject is still receiving clinical benefit from study treatment and that the potential benefit of continuing study treatment outweighs potential risk. Following Sponsor notification, subjects in combination treatment cohorts may be allowed to discontinue one component of study treatment but continue to receive the other. For cohorts where the initial dose is 40 mg cabozantinib, intra-subject dose escalation of cabozantinib from 40 mg to 60 mg is allowed after Sponsor approval for subjects who are tolerating the 40 mg

cabozantinib dose level well and have been treated on this dose level for at least 4 weeks. Subjects in the SAC and SAA cohorts who experience Investigator-assessed radiographic disease progression per RECIST 1.1 on single-agent therapy will be allowed to receive combination treatment with cabozantinib and atezolizumab provided they meet the eligibility criteria for combination treatment at that point (Second Agent Add-On Stage).

Post-Treatment Period: The final safety assessment will occur at the Post-Treatment Follow-Up Visit 30 (+14) days after the date of the decision to discontinue treatment. If a subject is experiencing an ongoing treatment-related AE that led to study treatment discontinuation, SAE, or AESI at the time of that visit, the subject will continue to be followed until the AE has resolved, the AE has improved to Grade 2 or lower, or the Investigator determines that the event has become stable or irreversible.

Maintenance Phase: The purpose of the Maintenance Phase is to continue to provide long-term access to study drug(s) to subjects who are deriving clinical benefit even after evaluation of the study objectives has been completed. When sufficient data have been collected to adequately evaluate all study endpoints, and upon site notification by the Sponsor, subjects remaining on study treatment or who have not completed the Post-Treatment Follow-Up Visit will enter the study Maintenance Phase. In the Maintenance Phase subjects who remain on treatment will continue to receive study treatment until a protocol-defined criterion for discontinuation has been met. Following Sponsor notification, subjects in combination treatment cohorts may be allowed to discontinue one component of study treatment but continue to receive the other.

In the Maintenance Phase, subjects are to undergo periodic safety assessments (including local laboratory tests) and tumor assessments; the nature and frequency of these assessments are to be performed per standard of care if allowed per local regulations. In order to continue to collect important safety information on subjects still enrolled in the study, reporting of SAEs; AEs (including irAEs), whether serious or not, leading to dose modifications or treatment discontinuation; AESIs; and other reportable events (pregnancy and medication errors with sequelae) is to continue per protocol requirements specific to the Maintenance Phase.

Assessments in the Post-Treatment Period (including the Post-Treatment Follow-Up Visit) are not required for subjects who discontinue study treatment in the Maintenance Phase (such subjects are to be followed per standard of care).

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

Study Completion by Country or by Site: After sufficient data have been collected to adequately evaluate all study endpoints and upon site notification by the Sponsor, the study will be considered complete at sites and in countries that no longer have active subjects.

**NUMBER OF SUBJECTS**

This study may enroll up to 1732 subjects with advanced solid tumors.

In the Dose-Escalation Stage, 9 to 36 subjects were planned to be enrolled. Enrollment for the Dose-Escalation Stage was completed prior to initiation of Protocol Amendment 2.0, and a total of 12 subjects have been treated with combination therapy.

In the Expansion Stage approximately 720 subjects may be treated with either combination therapy or single-agent therapy across 24 tumor-specific cohorts with each initially enrolling approximately 30 subjects except the SAA Cohort, which will initially enroll 10 subjects. Enrollment may be further extended in up to 10 Cohorts with up to an additional approximately 100 subjects each in the Combination-Therapy Cohorts and/or up to an additional approximately 50 subjects each in the SAC Cohorts in the Expansion Stage excluding the SAA Cohort upon the

SOC decision with a maximum additional enrollment of 1000 subjects. Extended enrollment beyond 30 subjects is not allowed in the SAA Cohort.

## TARGET POPULATION

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

*Of note, in the eligibility criteria described below, maintenance anticancer therapy after the initial anticancer therapy does not count towards the limit of prior systemic therapies, provided there is no tumor progression between the initial anticancer therapy and the start of maintenance anticancer therapy. In addition, radiosensitization chemotherapy and retreatment with the same anticancer agent do not count towards the limit of prior systemic therapies.*

*In the Expansion Stage, Cohorts 5 and 19 (UC) have identical eligibility criteria, as do Cohorts 7 and 20 (NSCLC) and Cohorts 21-23 (high risk CRPC).*

### *Inclusion Criteria*

1. Cytologically or histologically and radiologically confirmed solid tumor that is inoperable locally advanced, metastatic, or recurrent:

   Dose-Escalation Stage:

   a. Subjects with UC (including renal pelvis, ureter, urinary bladder, urethra) after prior platinum-based therapy, or

   b. Subjects with RCC (clear cell, non-clear cell histology) with or without prior systemic anticancer therapy

   Expansion Stage:

   c. Expansion Cohort 1**:** Subjects with RCC with clear cell histology (including those with mixed sarcomatoid component) and without prior systemic anticancer therapy for inoperable locally advanced or metastatic disease.

   d. Expansion Cohort 2**:** Subjects with UC with transitional cell histology (including renal pelvis, ureter, urinary bladder, urethra) who have radiographically progressed on or after platinum-containing chemotherapy including subjects who received prior neoadjuvant or adjuvant platinum-containing therapy with disease recurrence < 12 months from the end of last therapy.

   e. Expansion Cohort 3: Subjects with UC with transitional cell histology (including renal pelvis, ureter, urinary bladder, urethra) who are ineligible for cisplatin-based chemotherapy and have not received prior systemic anticancer therapy for inoperable locally advanced or metastatic disease.

      - *Ineligible for cisplatin-based chemotherapy is defined by meeting one of the following criteria:*

        *Impaired renal function (glomerular filtration rate [GFR] < 60 mL/min/1.73 $m^2$), hearing loss of ≥ 25 dB at two contiguous frequencies, or ≥ Grade 2 peripheral neuropathy per Common Terminology Criteria for Adverse Events (CTCAE) v4.*

      - *Prior neoadjuvant or adjuvant platinum-based chemotherapy is allowed if disease recurrence took place > 12 months from end of last therapy.*

f. Expansion Cohort 4: Subjects with UC with transitional cell histology (including renal pelvis, ureter, urinary bladder, urethra) eligible for cisplatin-based chemotherapy and have not received prior systemic anticancer therapy for inoperable locally advanced or metastatic disease.

   - *Prior neoadjuvant or adjuvant platinum-based chemotherapy is allowed if disease recurrence took place > 12 months from end of last therapy.*

g. Expansion Cohort 5: Subjects with UC with transitional cell histology (including renal pelvis, ureter, urinary bladder, urethra) who have radiographically progressed on or after one prior immune checkpoint inhibitor (anti-PD-1 or anti-PD-L1) for the treatment of inoperable locally advanced or metastatic disease.

   - *Allowed are up to 2 lines of prior systemic anticancer therapy to treat inoperable locally advanced or metastatic UC including prior treatment with an anti-CTLA-4 agent.*
   - *Excluded are subjects who had a prior combination therapy of an immune checkpoint inhibitor (anti-PD-1 or anti-PD-L1) with a VEGFR-targeting TKI.*

h. Expansion Cohort 6: Subjects with metastatic CRPC (adenocarcinoma of the prostate without small cell component; neuroendocrine differentiation and other histologic components are permitted if adenocarcinoma is the primary histology) who have radiographically progressed in soft tissue on or after enzalutamide and/or abiraterone acetate for metastatic disease.

   (Note: PSA progression or bone progression alone are not allowed to determine eligibility).

   - *Prior chemotherapy is not allowed with the exception of docetaxel given in combination with androgen deprivation therapy (ADT) for progressive castration-sensitive disease prior to treatment with enzalutamide and/or abiraterone acetate.*
   - *Subject must have castrate-level testosterone (< 50 ng/dL [< 1.73 nM]) following bilateral orchiectomy or by ongoing androgen deprivation therapy with a gonadotropin-releasing hormone (GnRH) analog that was initiated ≥ 4 weeks prior to first dose of study treatment and must be continued throughout the study.*

i. Expansion Cohort 7: Subjects with Stage IV non-squamous NSCLC who have radiographically progressed on or after treatment with one prior immune checkpoint inhibitor (anti-PD-1 or anti-PD-L1) for metastatic disease.

   - *Allowed are up to 2 lines of prior systemic anticancer therapy to treat metastatic NSCLC including prior treatment with an anti-CTLA-4 agent.*
   - *Excluded are subjects who had a prior VEGFR-targeting TKI*
   - *Excluded are subjects who have been diagnosed with an EGFR sensitizing mutation, ALK rearrangement, ROS1 rearrangement, or BRAF V600E mutation.*

j. Expansion Cohort 8: Subjects with Stage IV non-squamous NSCLC with positive PD-L1 expression (TC ≥ 1% [TC = tumor cell]) and without prior systemic anticancer therapy for metastatic disease.

   - *Acceptable reports for prior PD-L1 expression testing by immunohistochemical (IHC) assessment include the following:*
     - *US sites: FDA-approved Dako PD-L1 IHC 22C3 pharmDx assay*
     - *Ex-US sites: health authority-approved or CE-marked Dako PD-L1 IHC 22C3 pharmDx assay*

- *A prior local laboratory PD-L1 report using a validated assay may be accepted if slides can be provided to the central laboratory to assess PD-L1 expression using the FDA-approved Dako PD-L1 IHC 22C3 pharmDx assay.*

*Excluded are subjects who have been diagnosed with an EGFR sensitizing mutation, ALK translocation, ROS1 rearrangement, or BRAF V600E mutation.*

k. Expansion Cohort 9: Subjects with Stage IV nonsquamous NSCLC with documentation of a sensitizing EGFR mutation who have radiographically progressed during or following prior treatment with at least one EGFR-targeting TKI (eg, osimertinib, gefitinib, erlotinib, afatinib) for metastatic disease.

- *There is no limit on the number of prior lines of systemic anticancer therapy including chemotherapy for inoperable locally advanced, recurrent, or metastatic disease.*
- *Prior treatment with ICIs (anti-PD-1 or anti-PD-L1) is allowed if given in combination with chemotherapy.*

l. Expansion Cohort 10: Subjects with RCC with non-clear cell histology (including those with sarcomatoid component)

- *Allowed is prior therapy with up to one VEGFR-targeting TKI (eg, sunitinib, pazopanib) for inoperable locally advanced, recurrent, or metastatic disease.*
- *TKIs targeting MET or prior therapy with immune checkpoint inhibitors is not allowed.*

m. Expansion Cohort 11: Subjects with breast cancer that has tested negative for hormone epidermal growth factor receptor 2 (HER-2), estrogen receptors, and progesterone receptors (ie, triple-negative breast cancer [TNBC]) who have radiographically progressed during or following treatment with at least one prior systemic anticancer therapy for inoperable locally advanced, recurrent, or metastatic disease.

- *Allowed are up to 2 lines of prior systemic anticancer therapy for inoperable locally advanced, recurrent, or metastatic disease.*
- *Prior treatment with ICIs (anti-PD-1 or anti-PD-L1) is allowed.*
- *HER-2 negativity is defined as either of the following by local laboratory assessments:*
  - *In situ hybridization (ISH) non-amplified (ratio of HER-2 to CEP17 < 2.0 or single probe average HER-2 gene copy number < 4 signals/cell), or*
  - *IHC 0 or IHC 1+ (if more than one test result is available and not all results meet the inclusion criterion definition, all results should be discussed with the Sponsor to establish eligibility of the patient).*
- *Estrogen receptor (ER) and progesterone receptor (PR) negativity are defined as < 1% of cells expressing hormonal receptors via IHC analysis.*

n. Expansion Cohort 12: Subjects with epithelial ovarian cancer, including primary peritoneal cancer (PPC) and fallopian tube cancer (FTC) who have platinum-resistant or refractory disease.

- *Platinum- resistant disease is defined as disease progression within 6 months of receiving the last platinum dose. Platinum-refractory disease is defined as disease progression during platinum-based chemotherapy or within 4 weeks of the last platinum dose. Subjects who discontinue platinum-based*

*therapy due to an adverse event cannot be defined as platinum-resistant or refractory and are therefore not eligible.*

- *Allowed are up to 2 lines of prior systemic anticancer therapy for inoperable locally advanced, recurrent, or metastatic disease. Hormonal therapies and intraperitoneal anticancer therapies are not counted towards prior treatment restrictions.*
- *Ovarian borderline epithelial tumors (low malignant potential) are excluded.*

o. Expansion Cohort 13: Subjects with endometrial cancer of serous or endometrioid histology who have radiographically progressed during or following treatment with at least one prior systemic anticancer therapy for inoperable locally advanced, recurrent, or metastatic disease.

- *Allowed are up to 2 lines of prior systemic anticancer therapy for inoperable locally advanced, recurrent, or metastatic disease.*
- *Hormonal therapies are not counted towards prior treatment restrictions.*

p. Expansion Cohort 14: Subjects with advanced HCC who have a Child-Pugh score of A (Appendix L) and have not received prior systemic anticancer therapy for inoperable locally advanced, recurrent, or metastatic disease.

- *Subjects with active hepatitis B virus (HBV) infection (defined by HBsAg positive) must be on standard of care antiviral therapy and have HBV DNA < 500 IU/mL.*
- *Prior local-regional treatment (eg, radiofrequency ablation, transcatheter arterial chemoembolization [TACE]) is allowed.*

q. Expansion Cohort 15: Subjects with gastric cancer, gastroesophageal junction adenocarcinoma, or lower one-third esophageal adenocarcinoma who have radiographically progressed during or following platinum-containing or fluoropyrimidine-containing chemotherapy for inoperable locally advanced, recurrent, or metastatic disease.

- *Allowed are up to 2 lines of prior systemic anticancer therapy for inoperable locally advanced, recurrent, or metastatic disease.*
- *Prior HER-2/neu directed therapy is allowed.*

r. Expansion Cohort 16: Subjects with colorectal adenocarcinoma who have radiographically progressed during or following systemic chemotherapy that contained fluoropyrimidine in combination with oxaliplatin or irinotecan for metastatic disease.

- *Allowed are up to 2 lines of prior systemic anticancer therapy for inoperable locally advanced, recurrent, or metastatic disease.*
- *Prior EGFR-targeted therapy is allowed.*
- *Subjects with known microsatellite instability-high (MSI-H) and/or mismatch repair (MMR) deficient disease are excluded.*

s. Expansion Cohort 17: Subjects with head and neck cancer of squamous cell histology who have radiographically progressed during or following prior platinum-containing chemotherapy for inoperable locally advanced, recurrent, or metastatic disease.

- *Allowed primary tumor locations: oropharynx, oral cavity, hypopharynx, or larynx. Excluded are subjects with primary tumor site of the nasopharynx*
- *Allowed are up to 2 lines of prior systemic anticancer therapy for inoperable locally advanced, recurrent, or metastatic disease.*
- *Prior treatment with ICIs (anti-PD-1 or anti-PD-L1) is allowed.*
- *Prior EGFR-targeted therapy and radiotherapy concurrent or sequential with chemotherapy is allowed.*
- *Results from testing of HPV status for oropharyngeal cancers should be provided but are not required for eligibility.*

t. Expansion Cohort 18: Subjects with DTC (follicular, papillary, and poorly differentiated histologies) who are radioactive iodine (RAI) refractory or deemed ineligible for treatment with RAI.
   - *Subjects who have received prior systemic anticancer therapy for RAI-refractory disease are not allowed.*
   - *Subjects must be receiving thyroxine suppression therapy, and TSH must be below the lower cutoff of the reference range or less than 0.50 mIU/L (< 0.50 µIU/mL), whichever is lower, within 28 days before enrollment. (Note: If hormone replacement therapy is tolerated, a TSH level of ≤ 0.1 mIU/L(≤ 0.1 µIU/mL) should be targeted.)*

u. Exploratory Single-Agent Cabozantinib (SAC) Cohort 19: Subjects with UC with transitional cell histology (including renal pelvis, ureter, urinary bladder, urethra) who have radiographically progressed on or after one prior ICI (anti-PD-1 or anti-PD-L1) for the treatment of inoperable locally advanced or metastatic disease.
   - *Allowed are up to 2 lines of prior systemic anticancer therapy to treat inoperable locally advanced or metastatic UC including prior treatment with an anti-CTLA-4 agent.*
   - *Excluded are subjects who had a prior combination therapy of an ICI (anti-PD-1 or anti-PD-L1) with a VEGFR-targeting TKI.*

v. Exploratory Single-Agent Cabozantinib (SAC) Cohort 20: Subjects with Stage IV non-squamous NSCLC who have radiographically progressed on or after treatment with one prior ICI (anti-PD-1 or anti-PD-L1) for metastatic disease.
   - *Allowed are up to 2 lines of prior systemic anticancer therapy to treat metastatic NSCLC including prior treatment with an anti-CTLA-4 agent.*
   - *Excluded are subjects who had a prior VEGFR-targeting TKI*
   - *Excluded are subjects who have been diagnosed with an EGFR sensitizing mutation, ALK rearrangement, ROS1 rearrangement, or BRAF V600E mutation.*

w. Exploratory Single-Agent Cabozantinib (SAC) Cohort 21, Exploratory Single-Agent Atezolizumab (SAA) Cohort 22, and Combination-Therapy Expansion Cohort 23: Subjects with metastatic CRPC who have histologically or cytologically confirmed adenocarcinoma of the prostate without small cell component (Note: Neuroendocrine differentiation and other histologic components are permitted if adenocarcinoma is the primary histology) with the following requirements:

- Prior treatment with one, and only one, novel hormonal therapy (NHT) (eg, abiraterone, apalutamide, darolutamide, or enzalutamide) for castration-sensitive locally advanced (T3 or T4) or metastatic castration-sensitive prostate cancer (mCSPC), M0 CRPC, or mCRPC

  *Note: Subjects may have previously received taxane-based chemotherapy for mCSPC but no other approved or experimental nonhormonal systemic therapies for metastatic prostate cancer.*

- Bilateral orchiectomy or ongoing androgen deprivation therapy with a GnRH agonist/antagonist (surgical or medical castration), with serum testosterone ≤ 50 ng/dL (≤ 1.73 nmol/L) at screening
- Progressive disease at study entry as defined by at least one of the following two criteria:

  a. PSA progression defined by a minimum of 2 rising PSA values from 3 or 4 consecutive assessments with an interval of at least 7 days between assessments. The most recent qualifying PSA value must be drawn within 28 days of planned enrollment. (Note: If qualifying solely by PSA progression, the screening central lab PSA value must be at least 2 ng/mL [2 µg/L] but need not serve as last PSA value for determination of PSA progression; up to one PSA decrease is permitted as long as it is not the most recent value), OR

  b. Soft tissue disease progression in the opinion of the Investigator. Note: Bone disease progression alone does not qualify.

- High risk metastatic disease per Investigator read as defined by at least one of the following:

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

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

x. Combination-Therapy Expansion Cohort 24: Subjects with metastatic CRPC who have histologically or cytologically confirmed adenocarcinoma of the prostate without small cell component (Note: Neuroendocrine differentiation and other histologic components are permitted if adenocarcinoma is the primary histology.) with the following requirements:

- Prior taxane-based chemotherapy initiated for mCRPC (Note: Subjects may or may not have previously received docetaxel for mCSPC)
- Prior treatment with at least one NHT (eg, abiraterone, apalutamide, darolutamide, or enzalutamide) for castration-sensitive locally advanced (T3 or T4) or metastatic castration-sensitive prostate cancer (mCSPC), M0 CRPC, or mCRPC.
- Bilateral orchiectomy or ongoing androgen deprivation therapy with a GnRH agonist/antagonist (surgical or medical castration), with serum testosterone ≤ 50 ng/dL (≤ 1.73 nmol/L) at screening.
- 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 consecutive assessments with an interval of at least 7 days between assessments. The most recent qualifying PSA value must be drawn within 28 days of planned enrollment. (Note: If

qualifying solely by PSA progression, the screening central lab PSA value must be at least 2 ng/mL [2 µg/L] but need not serve as last PSA value for determination of PSA progression; up to one PSA decrease is permitted as long as it is not the most recent value), OR

b. Soft tissue disease progression in the opinion of the Investigator. Note: Bone disease progression alone does not qualify.

- High risk metastatic disease per Investigator read as defined by at least one of the following:

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

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

2. Measurable disease per RECIST 1.1 as determined by the Investigator. Measurable disease must be outside the radiation field if prior radiation therapy was administered.

3. Tumor tissue material available (archival or recent tumor biopsy).

   *NOTE: Subjects in Cohorts 6 and 21-23 are exempt from this criterion if no archival tissue is available and subjects are unwilling to undergo a fresh tumor biopsy or a fresh biopsy is not safely obtainable.*

4. Recovery to baseline or ≤ Grade 1 CTCAE v4 from toxicities related to any prior treatments, unless AE(s) are clinically nonsignificant and/or stable on supportive therapy.

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

6. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1.

7. Adequate organ and marrow function, based upon meeting all of the following laboratory criteria within 14 days before first dose of study treatment:

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

   b. White blood cell count ≥ 2500/µL (≥ $2.5 \times 10^9$/L).

   c. Platelets ≥ 100,000/µL (≥ $100 \times 10^9$/L) without transfusion within 2 weeks before screening laboratory sample collection. For subjects with HCC ≥ 75,000/µL (≥ $75 \times 10^9$/L).

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

   e. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) ≤ 3 × upper limit of normal (ULN). ALP ≤ 5 × ULN with documented bone metastases. For subjects with HCC: ALT, AST, and ALP ≤ 5 × ULN. For subjects with mCRPC with documented bone metastases: ALT ≤ 3 × ULN, AST ≤ 3 × ULN, and ALP ≤ 10 × ULN. If ALP > 5 × ULN in mCRPC subjects, then it must be demonstrated that it is predominantly bone-specific ALP.

   f. Total bilirubin ≤ 1.5 × ULN (for subjects with Gilbert's disease ≤ 3 × ULN). For subjects with HCC ≤ 2 mg/dL (≤ 34.2 µmol/L).

   g. Serum creatinine ≤ 1.5 × ULN or calculated creatinine clearance ≥ 40 mL/min (≥ 0.67 mL/sec) using the Cockcroft-Gault equation (see Table 5-2 for Cockcroft-Gault formula).

   h. Urine protein/creatinine ratio (UPCR) ≤ 1 mg/mg (≤ 113.2 mg/mmol). For subjects with UC: ≤ 2 mg/mg (≤ 226.4 mg/mmol) creatinine.

8. Capable of understanding and complying with the protocol requirements and must have signed the informed consent document.
9. 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 (defined in Appendix K) during the course of the study and for 5 months after the last dose of study treatment. An additional contraceptive method, such as a barrier method (eg, condom), is recommended.
10. Female subjects of childbearing potential must not be pregnant at screening. Female subjects are considered to be of childbearing potential unless one of the following criteria is met: permanent sterilization (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) or documented postmenopausal status (defined as 12 months of amenorrhea in a woman over 45 years-of-age in the absence of other biological or physiological causes. In addition, females under 55 years-of-age must have a serum follicle stimulating hormone (FSH) level > 40 mIU/mL to confirm menopause). Note: Documentation may include review of medical records, medical examination, or medical history interview by study site staff.

***Exclusion Criteria***

1. Prior treatment with cabozantinib or ICIs including anti-CTLA-4, anti-PD-1, anti-PD-L1, anti-PD-L2, anti-OX-40, anti-CD137 therapy except for Expansion Cohorts 5, 7, 9, 11, and 17, and SAC Cohorts 19 and 20 in which prior anti-PD-1 or anti-PD-L1 therapy is required and/or allowed for eligibility (see Inclusion Criteria 1g, 1i, 1k, 1m, 1s, 1v, and 1w, respectively, for details).
2. Receipt of any type of small molecule kinase inhibitor (including investigational kinase inhibitor) within 2 weeks before first dose of study treatment. EGFR targeted TKIs are allowed to be continued until 5 days prior to first dose of study treatment in Expansion Cohort 9.
3. For mCRPC subjects (Expansion Cohorts 6 and 23-24, Exploratory SAC Cohort 21, and Exploratory SAA Cohort 22): receipt of abiraterone within 1 week before first dose of study treatment or receipt of any other androgen-receptor inhibitors within 2 weeks before first dose of study treatment.
4. HCC subjects who meet any of the following criteria are ineligible:
    a. Received prior local anticancer therapy (including embolization and ablation) within 4 weeks before first dose of study treatment. For prior radiation for bone metastases, refer to Exclusion Criteria 6.
    b. Subjects with fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma.
5. Receipt of any type of anticancer antibody (including investigational antibody) or systemic chemotherapy within 4 weeks before first dose of study treatment except for Expansion Cohorts 5, 7, 9, 11, and 17, and SAC Cohorts 19 and 20 in which receipt of a PD-1, PD-L1, or CTLA-4 targeting antibody is permitted within 4 weeks before first dose of study treatment.
6. Radiation therapy for bone metastasis within 2 weeks, any other local radiation therapy within 4 weeks before first dose of study treatment. Subjects who have received systemic treatment with radionuclides within 6 weeks before first dose of study treatment are not eligible. Subjects with clinically relevant ongoing complications from prior radiation therapy are not eligible.
7. Known brain metastases or cranial epidural disease unless adequately treated with radiotherapy and/or surgery (including radiosurgery) and stable for at least 4 weeks before first dose of study treatment. Eligible subjects must be neurologically asymptomatic and without corticosteroid treatment at the time of first dose of study treatment.
8. Concomitant anticoagulation with oral anticoagulants 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 specified direct factor Xa inhibitors rivaroxaban, edoxaban, or apixaban in subjects (excluding HCC subjects) without known brain metastases who are on a stable dose of the anticoagulant for at least 1 week before first dose of study treatment and without clinically significant hemorrhagic complications from the anticoagulation regimen or the tumor.

            *Note: Subjects with HCC may be treated with therapeutic LMWH but must have a screening platelet count > 100,000/μL. Direct inhibitors of thrombin or factor Xa are not permitted in subjects with HCC.*
9. Diagnosis of immunodeficiency or is receiving systemic steroid therapy (> 10 mg daily prednisone equivalent) or any other form of immunosuppressive therapy within 2 weeks prior to first dose of study treatment. Inhaled,

intranasal, intraarticular, and topical corticosteroids and mineralocorticoids are allowed.
*Note: Adrenal replacement steroid doses > 10 mg daily prednisone equivalent are permitted in the absence of active autoimmune disease. Transient short-term use of systemic corticosteroids for allergic conditions (eg, contrast allergy) is also allowed.*

10. Administration of a live, attenuated vaccine within 30 days before first dose of study treatment.
11. The subject has uncontrolled, significant intercurrent or recent illness including, but not limited to, the following conditions:
    a. Cardiovascular disorders:
        i. Congestive heart failure New York Heart Association Class 3 or 4, unstable angina pectoris, serious cardiac arrhythmias.
        ii. Uncontrolled hypertension defined as sustained blood pressure (BP) > 140 mm Hg systolic or > 90 mm Hg diastolic despite optimal antihypertensive treatment.
        iii. Stroke (including transient ischemic attack [TIA]), myocardial infarction (MI), or other ischemic event, or thromboembolic event (eg, deep venous thrombosis [DVT], pulmonary embolism [PE]) within 6 months before first dose. Upon Sponsor approval, subjects with a diagnosis of incidental, subsegmental PE or DVT within 6 months are allowed if stable, asymptomatic, and treated with anticoagulation for at least 1 week before first dose. Iatrogenic arterial embolization procedures such as tumor arterial embolization or splenic artery embolization are allowed.
    b. Gastrointestinal (GI) disorders including those associated with a high risk of perforation or fistula formation:
        i. Tumors invading the GI-tract, active peptic ulcer disease, inflammatory bowel disease, diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis or acute obstruction of the pancreatic or biliary duct, or gastric outlet obstruction. Presence of primary GI tumor is not excluded.
        ii. Abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess within 6 months before first dose. Note: Complete healing of an intra-abdominal abscess must be confirmed before first dose.
        iii. Gastric or esophageal varices that are untreated or incompletely treated with bleeding or high risk for bleeding. Subjects treated with adequate endoscopic therapy (according to institutional standards) without any episodes of recurrent GI bleeding requiring transfusion or hospitalization for at least 6 months prior to study entry are eligible.
    c. Clinically significant hematuria, hematemesis, or hemoptysis of > 0.5 teaspoon (2.5 mL) of red blood, or other history of significant bleeding (eg, pulmonary hemorrhage) within 12 weeks before first dose.
    d. Cavitating pulmonary lesion(s) or known endobronchial disease manifestation.
    e. Lesion invading a major blood vessel including, but not limited to, inferior vena cava, pulmonary artery, or aorta. HCC subjects with lesions invading the hepatic portal vasculature are eligible.
    f. Other clinically significant disorders such as:
        i. Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, psoriatic arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener

granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, or multiple sclerosis (see Appendix E for a more comprehensive list of autoimmune diseases and immune deficiencies). Subjects with the following conditions are eligible for the study:

- A history of autoimmune-related hypothyroidism and on thyroid replacement hormone therapy

  *Note: Subjects with prior history of thyroiditis are allowed if they have undergone sub-total, near-total, or total thyroidectomy.*

- Controlled Type 1 diabetes mellitus and on an insulin regimen
- Asthma
- Eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only provided all of following are true:
  - Rash covers < 10% of body surface area
  - Disease is well controlled at baseline and requires only low-potency topical corticosteroids
  - No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high potency or oral corticosteroids within the previous 12 months

ii. Active infection requiring systemic treatment, infection with human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness, acute or chronic hepatitis B or C infection in non-HCC tumor cohorts, or a known positive test for tuberculosis infection if supported by clinical or radiographic evidence of disease. Subjects with history of COVID-19 must have recovered from the disease at least 30 days prior to enrollment.

iii. History of idiopathic pulmonary fibrosis, organizing pneumonia (eg, bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computerized tomography (CT) scan. History of radiation pneumonitis in the radiation field (fibrosis) is permitted.

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

v. Malabsorption syndrome.

vi. For all subjects except Cohort 18 (DTC): Free thyroxine (FT4) outside the laboratory normal reference range. Asymptomatic subjects with FT4 abnormalities can be eligible after sponsor approval.

vii. Moderate to severe hepatic impairment for subjects with chronic liver disease (Child-Pugh B or C; Appendix L).

viii. Requirement for hemodialysis or peritoneal dialysis.

ix. History of solid organ or allogenic stem cell transplant.

12. Major surgery (eg, GI surgery, removal or biopsy of brain metastasis) within 4 weeks or minor surgery (eg, simple excision, tooth extraction) within 10 days before first dose of study treatment. Complete wound healing from surgery must have occurred before first dose. Subjects with clinically relevant ongoing complications from prior surgery are not eligible.
13. Corrected QT interval calculated by the Fridericia formula (QTcF) > 500 ms per electrocardiogram (ECG) within 14 days before first dose of study treatment (see Section 5.6.4 for Fridericia formula).

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

14. Pregnant or lactating females.
15. Inability to swallow tablets.
16. Previously identified allergy or hypersensitivity to components of the study treatment formulations. *Subjects with a history of infusion-related reaction to prior therapy with atezolizumab may be eligible by sponsor approval if the reaction was considered mild and manageable with appropriate supportive care (eg, use of premedication according to standard of care).*
17. Diagnosis of another malignancy within 2 years before first dose of study treatment, except for superficial skin cancers, or localized, low grade tumors deemed cured and not treated with systemic therapy. Incidentally diagnosed prostate cancer is allowed if assessed as stage ≤ T2N0M0 and Gleason score ≤ 6.

**ESTIMATED LENGTH OF SUBJECT PARTICIPATION**

It is estimated that subjects with advanced previously treated GC/GEJC/LEC may receive study treatment for an average of 4 months, subjects with advanced previously treated UC, CRPC, NSCLC, OC, EC, or untreated HCC may receive study treatment for an average of 6 months, and subjects with advanced treatment-naïve UC, RCC, NSCLC, or DTC may receive study treatment for an average of 9 months. Subjects will however be followed until death, withdrawal of consent, or Sponsor decision to no longer collect survival data.

**ESTIMATED STUDY DURATION**

It is estimated that 6 months will be required to enroll the subjects and determine the recommended dose and schedule in the Dose-Escalation Stage. It is estimated that approximately 24 months will be required to enroll the 20 Combination-Therapy Expansion Cohorts, three Exploratory SAC Cohorts, and one Exploratory SAA Cohort in the Expansion Stage. The true intervals required to meet the milestones above may be longer or shorter due to the impact of the global COVID-19 pandemic on subject enrollment and other aspects of study conduct.

**INVESTIGATIONAL REGIMEN DOSE/ ROUTE/ INTERVAL**

Cabozantinib will be supplied as 60-mg and 20-mg tablets (expressed as freebase weight). In the Dose-Escalation Stage, cabozantinib was administered orally daily at dose levels of 20, 40, or 60 mg.

Atezolizumab will be administered at a standard dosing regimen of 1200 mg as an IV infusion once every 3 weeks (q3w). The initial infusion of atezolizumab will be given over 60 (± 15) minutes without premedication for potential IRRs or CRS. Subsequent IV infusions may be given over 30 (± 10) minutes if the initial infusion is tolerated. Premedication for infusion-reaction is allowed after the initial infusion. No bolus or IV push of atezolizumab is allowed.

Initial cohorts in the Dose-Escalation Stage received the combination regimen on a Standard Dosing Schedule with the first infusion of atezolizumab given on the same day as the first dose of cabozantinib.

The Cohort Review Committee could have decided to enroll additional cohorts in the Dose-Escalation Stage on a Cabozantinib Run-In Dosing Schedule with the first infusion of atezolizumab given on Cycle 2 Day 1 (C2D1), 21 days after their first dose of single-agent cabozantinib. Prior to Protocol Amendment 2.0 the recommended dose for the Expansion stage had already been identified (combination treatment of 40 mg cabozantinib qd orally plus

1200 mg atezolizumab q3w IV) during the Escalation Stage using the Standard Dosing Schedule. The Cabozantinib Run-In Dosing Schedule will therefore not be implemented in the study.

In the Expansion Stage, all initially enrolled subjects in the Combination-Therapy Cohorts and any additional subjects enrolled per Extended Enrollment Option 1 will receive cabozantinib 40 mg in combination with the standard dose of atezolizumab. Additional subjects enrolled per Extended Enrollment Option 2 will receive cabozantinib 60 mg in combination with the standard dose of atezolizumab. For details on the Extended Enrollment Options, see Section 3.5.2.1. In addition, intra-subject dose escalation of cabozantinib from 40 mg to 60 mg is allowed after Sponsor approval for subjects enrolled at the 40-mg cabozantinib dose level who are tolerating the 40 mg cabozantinib dose level well and have been treated on this dose level for at least 4 weeks.

Subjects in the SAC Cohorts will receive cabozantinib 60 mg qd.

Subjects in the SAA Cohort will receive the standard dosing regimen of atezolizumab (1200 mg IV, q3w).

Subjects who radiographically progress (per Investigator per RECIST 1.1) on single-agent treatment in the SAC or SAA Cohorts may be able to receive combination treatment with cabozantinib and atezolizumab in the Second Agent Add-On Stage if they are deemed eligible (see Section 3.5.2.4). These subjects will receive atezolizumab doses of 1200 mg IV q3w and cabozantinib doses at the lower of 40 mg PO qd or their most recently received dose level.

Refer to Section 6.5.1 for management guidance on dose reductions and/or dose interruptions due to an AE in the Dose-Escalation and Expansion Stages.

**SAFETY ASSESSMENTS**

Safety evaluations will include assessments of AEs (including irAEs and AESIs), vital signs, ECGs, laboratory tests, and concomitant medications. Adverse event seriousness, severity grade, relationship to study treatment, and relationship to immune effects (ie, irAEs) will be assessed by the investigator. Severity grade will be defined by the NCI CTCAE version 4.

**TUMOR ASSESSMENTS**

Tumor response will be assessed using RECIST 1.1 (Appendix G). Additional exploratory efficacy evaluation will include the application of irRECIST for immune response (Appendix H). Subjects will be assessed using a magnetic resonance imaging (MRI) or a CT scan from the date of the first dose of study treatment until the later of radiographic disease progression per RECIST 1.1 as determined by the investigator or the date of the decision to permanently discontinue study treatment. Radiographic tumor assessments will continue on the protocol-defined schedule, regardless of whether study treatment is reduced, interrupted, delayed, or discontinued.

Chest / Abdomen / Pelvis/ Neck: Unless otherwise described, CT of Chest/Abdomen/Pelvis (CAP) or CT chest and MRI abdomen/pelvis will be performed in all subjects at screening and every 6 weeks (± 5 days) after initiation of study treatment throughout the first 12 months on study. Upon completion of 12 months on study, these assessments will be performed every 12 weeks (± 7 days). For subjects with DTC and head & neck cancer, CT/MRI of the neck will be performed in addition to the CAP assessments. Subjects with head & neck cancer will be using the same imaging schedule after screening. For subjects with DTC the imaging frequency after screening will be every 9 weeks after initiation of study treatment throughout the first 12 months on study; upon completion of 12 months on study, these assessments will be performed every 12 weeks (± 7 days). Low dose non-contrast CT images from combined positron emission tomography/computed tomography (PET/CT) imaging cannot be used for tumor evaluations in this study.

Brain: MRI (or CT) of the brain will be performed at screening in all subjects with RCC, head and neck cancer, and NSCLC and for subjects with the other tumor indications who have a history or clinical symptoms of brain metastasis. After study treatment initiation MRI (or CT) scans of the brain are only required in subjects with documented, treated brain metastasis or if clinically indicated by signs and symptoms suggestive of new central nervous system (CNS) metastases. Assessments after the first dose of study treatment will be performed every 12 weeks (± 7 days). MRI is the preferred imaging method for brain. If CT of the brain is performed instead of MRI, ambiguous results must be confirmed by MRI unless contraindicated. Subjects without documented brain metastasis during the screening assessment are not required to undergo brain imaging after initiating study treatment unless clinically indicated. In order to meet the eligibility requirements of the study, brain metastasis must have been treated and stable for at least 4 weeks before first dose of study treatment.

Bone scans: Technetium bone scans (TBS) will be performed at screening in all subjects with CRPC and for subjects with the other tumor indications who have a history or clinical symptoms (ie, bone pain) of bone metastases. After study treatment initiation bone scans are only required in subjects with documented bone lesions or if clinically indicated by signs and symptoms suggestive of new bone metastases. Assessments after the first dose will follow routine clinical practice (approximately every 12 weeks throughout the first 12 months and every 24 weeks thereafter). Lesions identified on bone scan are not to be recorded as target, non-target, or new lesions. Bone scan findings alone cannot be used for the determination of progression or response in this study and need to be corroborated by CT/MRI. Bone lesions corroborated by CT/MRI must be reported as non-target or new lesions. PET scan or plain films are not considered adequate imaging techniques to measure bone lesions.

Subjects enrolled in the SAC or SAA cohorts who experience Investigator-assessed radiographic progression per RECIST 1.1 may be eligible to receive the combination therapy in the Second Agent Add-On Stage (see Section 3.5.2.4 for more details). A new baseline tumor status will be established for these subjects based upon their most recent set of scans performed prior to receiving the first dose of the second agent in the Second Agent Add-On Stage; if these scans were taken > 4 weeks prior to first dose of the second agent, new scans will be required to establish the baseline.

For the purpose of determining radiographic study endpoints for selected cohorts, central review of radiographic images may be conducted by a BIRC. All protocol-required radiographic tumor assessments for these selected cohorts will be sent to the BIRC, which also will review prior radiation history data and prior local therapy information for the purpose of selection of target lesions. Details are provided in the Imaging Manual.

**TUMOR MARKER ASSESSMENTS**

For subjects with CRPC, HCC, OC, CRC, and DTC, tumor marker samples (ie, PSA, alpha-feta protein [AFP], CA125, carcinoembryonic antigen [CEA], and thyroglobulin, respectively) will be collected at screening, Day 1 of every third cycle (or every 9 weeks, whichever is earlier) for the first 12 months on study, and then Day 1 of every fifth cycle (or every 15 weeks, whichever is earlier) until the earlier of initiation of subsequent systemic anticancer therapy or permanent loss to radiographic follow-up (including hospice admission). For subjects with CRPC who receive combination treatment in the Second Agent Add-On Stage, PSA samples will be collected at screening for that stage, Day 1 of every third cycle on that stage (or every 9 weeks, whichever is earlier) for the first 12 months, and then Day 1 of every fifth cycle of that stage (or every 15 weeks, whichever is earlier) until the earlier of initiation of subsequent systemic anticancer therapy or permanent loss to radiographic follow-up (including hospice admission). The tumor marker assessments will not be used to determine progressive disease or to make study treatment decisions in this study.

## OVERALL SURVIVAL FOLLOW-UP ASSESSMENTS

Subjects will be contacted (eg, in person or by telephone) approximately every 12 weeks (± 14 days) after the Post-Treatment Follow-Up Visit to assess survival status and to document receipt of subsequent anticancer therapy unless consent to participate in survival follow-up is withdrawn or the Sponsor deems sufficient efficacy data have been collected for the study.

## PHARMACOKINETIC ASSESSMENTS

Dose-Escalation Stage:

Blood samples for PK analysis will be obtained on the date of first dose of study treatment (C1D1; prior to study treatment administration [cabozantinib and atezolizumab], approximately 5 min after completion of the atezolizumab infusion, and at 2 h, 4 h, and 6-8 h after cabozantinib dosing), and prior to study treatment dosing on C1D10, C2D1, and C3D1.

Expansion Stage:

*Combination Therapy Expansion Cohorts:*

Blood samples for PK analysis will be obtained for plasma cabozantinib and serum atezolizumab concentration measurement on the date of first dose of study treatment (C1D1; prior to study treatment administration [cabozantinib and atezolizumab], approximately 5 min after completion of the atezolizumab infusion, and 2 h after the first dose of cabozantinib) and prior to study treatment dosing (atezolizumab infusion) on C2D1 and C3D1.

*Exploratory SAC Cohorts:*

Blood samples for PK analysis will be obtained for plasma cabozantinib on the date of first dose of cabozantinib treatment (C1D1; prior to cabozantinib treatment administration) and on C2D1 and C3D1.

*Exploratory SAA Cohort:*

Blood samples for PK analysis will be obtained for serum atezolizumab concentration measurement on the date of first dose of study treatment (C1D1; prior to study treatment administration, approximately 5 min after completion of the atezolizumab infusion) and prior to study treatment dosing on C2D1 and C3D1.

In the Dose-Escalation Stage and for the Combination-Therapy Cohorts in the Expansion Stage, samples will be analyzed for the plasma concentration of cabozantinib and the serum concentrations of atezolizumab. Only the PK of cabozantinib will be assessed for subjects in the SAC Cohorts, and only the PK of atezolizumab will be assessed for subjects in the SAA Cohort. PK will not be assessed in subjects who receive combination therapy after progression on single agent therapy (Second Agent Add-On Stage).

## IMMUNOGENICITY ASSESSMENTS

Blood samples will be obtained from all subjects in the combination treatment cohorts and subjects in the Exploratory SAA Cohort in the Expansion Stage for immunogenicity assessment predose on C1D1, C3D1, C7D1, and at the Post-Treatment Follow-up Visit.

For subjects who radiographically progress per RECIST 1.1 on single-agent therapy in the SAC Cohorts and transition to combination therapy, blood samples for immunogenicity assessments will be collected predose on Add on Cycle 1 Day 1 (aoC1D1), aoC3D1, and aoC7D1 in the Second Agent Add-On Stage and at the Post Treatment Follow-up Visit. For subjects who radiographically progress per RECIST 1.1 on single-agent therapy in

the SAA Cohort and transition to combination therapy, a blood sample for immunogenicity assessment will be collected at the Post Treatment Follow-up Visit.

## BIOMARKER ASSESSMENTS

Peripheral blood and tumor tissue will be collected and may be assessed for exploratory biomarker analyses. Peripheral blood samples will be obtained as specified in the Schedule of Assessments. Tumor tissue (archival) will be obtained prior to first dose of study treatment, and optional fresh tumor tissue biopsies may also be performed. Exploratory analyses may include the following:

- MET, AXL, and PD-L1 in tumor specimens for association with clinical outcomes
- Immune cell infiltration and tumor characteristics (ie, mutational load assessment) in tumor specimens and blood for association with clinical outcome
- Circulating immune cells in peripheral blood (ie, lymphocyte subset analyses by flow cytometry)
- Blood biomarkers (ie, cytokines/chemokines, VEGF)
- Evaluation of MMR and MSI status

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

For NSCLC subjects, available tumor mutation analysis reports (indicating EGFR status) should be provided at screening. For eligibility review for Expansion Cohort 8, prior PD-L1 reports from tests using the FDA approved pharmDx PD-L1 22C3 kits should be provided early in screening.

## STATISTICAL METHODS

### Combination Therapy Cohorts:

Dose-Escalation Stage:

The number of subjects per dose escalation cohort has been chosen based on a well-established Phase 1 dose-escalation trial design. Subjects are accrued into cohorts in a “3 plus 3” fashion with each cohort consisting initially of 3 subjects and potentially expanding to 6 subjects based upon the number of DLTs observed. A total of 9 to 36 subjects are expected to be enrolled in this stage, depending upon the number of escalation cohorts and subjects required to establish an MTD or recommended Expansion Stage dose and schedule.

Summaries will focus on AEs and tumor response by cohort. A narrative will also be prepared to describe the accrual and expansion of dose-escalation cohorts, subject replacement, the DLTs observed, Cohort Review Committee decisions and the final rationale for the recommended Expansion Stage dose and schedule. For exploratory purposes, the ORR as assessed by investigator per RECIST 1.1 will be presented descriptively for each dose-escalation cohort.

Expansion Stage:

*Combination-Therapy Expansion Cohorts*

*Objective Response Rate*: The objective of the Expansion Stage is to estimate ORR, defined as the proportion of subjects with a confirmed complete response (CR) or partial response (PR) per RECIST 1.1 as determined by the investigator. ORR will be evaluated independently within each of the Combination-Therapy Expansion Cohorts.

The primary purpose of estimating ORR in the Combination-Therapy Cohorts in the Expansion Stage is to assess if the true response rate with this combination regimen is better than that expected with monotherapy. Thus, 2-sided

80% and 60% Blyth-Still-Casella confidence intervals (CIs) will be constructed for ORR, providing 90% and 80% 1-sided confidence, respectively, when interpreting the lower bound. The sample size of 30 subjects for each of the Expansion Cohorts was chosen to ensure the lower bound of the 2-sided 80% CI extended no more than 12 percentage points from the point estimate.

Combination-Therapy Expansion Cohorts may enroll additional subjects beyond the initial subjects per Extended Enrollment Option 1 or 2 (described below). It is anticipated that not all Expansion Cohorts will open for additional enrollment. Note: Up to 10 cohorts (including SAC Cohorts) may be expanded in the Expansion Stage; extended enrollment beyond 30 subjects is not allowed in the SAA Cohort.

Extended Enrollment Option 1: Should the SOC deem that a clinically meaningful ORR has been observed in an Expansion Cohort, approximately 100 new subjects may be added to that cohort to further investigate the safety and clinical benefit of the combination in that treatment setting.

Decisions by the SOC regarding the clinical significance of the achieved ORR in Expansion Cohorts will include an evaluation of the lower bound of confidence intervals for ORR in the initially enrolled approximately 30 subjects, and the expansion cohorts will be extended as follows:

Extension-Part I: Approximately 50 additional subjects will be added in this extension part for a total of approximately 80 subjects in an expansion cohort. The observed ORR in the previously enrolled subjects will be considered. A minimum observed ORR of around 20% or more will be used as a target (though not a requirement) for the SOC to consider cohort expansion. This corresponds to 80% confidence that the true ORR is ≥ 13% for n = 30 (≥ 11% for n = 15). The magnitude of ORR deemed clinically meaningful by the SOC may vary by cohort, and the committee may consider other factors of clinical benefit (eg, time to response, duration of response, safety/tolerability) in the decision to extend enrollment.

Extension-Part II: Approximately 50 additional subjects will be added in this second extension part for a maximum total of approximately 130 subjects in an expansion cohort. The observed ORR for the previously enrolled subjects (approximately 30 subjects initially enrolled + approximately 50 subjects enrolled in Extension-Part I) will be considered. A minimum observed ORR of around 35% or more will be used as a target for the SOC to consider additional cohort expansion. This corresponds to 90% confidence that the true ORR is ≥ 28% for n = 80. Part II extension will only apply to tumor indications with a high-unmet medical need and very encouraging efficacy and safety data observed in Part I.

A total sample size of 130 subjects was selected to ensure the lower bound of the 95% confidence interval for ORR will extend less than 10% points from the point estimate if Part II is implemented.

Extended Enrollment Option 2: For Expansion Cohorts in which the initially enrolled approximately 30 subjects do not meet the criteria for Extended Enrollment Option 1, the SOC may decide to allow each selected Expansion Cohort to enroll approximately 30 new subjects to receive the highest dose level of cabozantinib explored in the Dose-Escalation Stage (60 mg) in combination with atezolizumab 1200 mg to explore whether the higher cabozantinib dose will lead to improved clinical activity and maintain an acceptable safety profile.

*PFS and OS*: Median PFS and OS will be estimated using Kaplan-Meier methods.

*DOR*: DOR medians will be estimated using Kaplan-Meier analysis and will be limited to patients who experienced a confirmed objective response.

*Safety*: Summaries of AEs, irAEs, AESIs, and SAEs will be tabulated by cohort according to system organ class and preferred term by overall incidence; worst reported severity; and relationship to study treatment. Selected laboratory test results will be summarized by treatment group to evaluate worst post-baseline CTCAE grade and shifts or changes from baseline.

**Exploratory Single-Agent Cabozantinib (SAC) Cohorts:**

SAC Cohorts 19, 20, and 21 will each initially enroll approximately 30 subjects in UC, NSCLC, and CRPC cohorts, respectively, with a potential to enroll up to approximately 50 additional subjects in each cohort per the SOC. As discussed in Section 3.5.2.4, subjects who exhibit Investigator-assessed radiographic progression per RECIST 1.1 following treatment with single-agent cabozantinib may be eligible to receive combination therapy (Second Agent Add-On Stage). Separate analyses of safety and efficacy will be performed for subjects who receive combination treatment after progressing on single-agent cabozantinib.

All analyses conducted for these cohorts will be presented for descriptive purposes. No formal comparisons to other study cohorts are planned. Median duration and corresponding 95% CI will be estimated using Kaplan-Meier method for PFS and OS. Objective response rate will also be estimated. Descriptive statistics such as frequency and percent will be presented for safety endpoints described in Section 9.3.1.

**Exploratory Single-Agent Atezolizumab (SAA) Cohort:**

SAA Cohort 22 will initially enroll 10 subjects with advanced CRPC. Additional enrollment will be conditional upon responses observed among the first 10 enrolled subjects. If there are at least two confirmed responses (PR or CR) per RECIST 1.1 among the initial 10 enrolled subjects, up to 20 additional subjects may be enrolled for a maximum total of 30 subjects. Extended enrollment beyond 30 subjects is not allowed in this cohort. As discussed in Section 3.5.2.4, subjects who exhibit Investigator-assessed radiographic progression per RECIST 1.1 following treatment with single-agent atezolizumab may be eligible to receive combination therapy (Second Agent Add-On Stage). Separate analyses of efficacy and safety will be performed for subjects who receive combination treatment after progressing on single-agent atezolizumab.

All analyses conducted for these subjects will be presented for descriptive purposes. No formal comparisons to other study cohorts are planned. Median duration and corresponding 95% CI will be estimated using Kaplan-Meier method for PFS and OS. Objective response rate will also be estimated. Descriptive statistics such as frequency and percent will be presented for safety endpoints described in Section 9.3.1.

**Second Agent Add-On Stage:**

All analyses conducted for subjects treated in the Second Agent Add-On Stage will be presented for descriptive purposes. No formal comparisons to other study cohorts are planned. Radiographic endpoints will be assessed relative to the new baseline established at entry to the Single Agent Add-On Stage. Median duration and corresponding 95% CI will be estimated using Kaplan-Meier method for PFS. Objective response rate will also be estimated. Descriptive statistics such as frequency and percent will be presented for safety endpoints described in Section 9.3.1.

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| | |
|---|---|
| ACTH | adrenocorticotropic hormone |
| 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 |
| aoC#D# | Add-On Cycle # Day # |
| AST | aspartate aminotransferase |
| AUC | area under the plasma drug concentration-vs-time curve |
| aoW#D# | Add-on Week # Day # |
| BIRC | Blinded Independent Radiology Committee |
| BP | blood pressure |
| BSR | bone scan response |
| BUN | blood urea nitrogen |
| C#D# (eg, C1D1) | Cycle # Day # |
| CAP | chest/abdomen/pelvis |
| CFR | Code of Federal Regulations |
| CI | confidence interval |
| CNS | central nervous system |
| CR | complete response |
| CRC | colorectal cancer |
| CRF | case report form |
| CRPC | castration-resistant prostate cancer |
| CRS | cytokine-release syndrome |
| CT | computerized tomography |
| CTC | circulating tumor cell |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTEP | Cancer Therapy Evaluation Program |
| CYP | cytochrome P450 |
| ddMVAC | dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin |
| DILI | drug-induced liver injury |
| DLT | dose-limiting toxicity |
| DOR | duration of response |
| DVT | deep vein thrombosis |
| EC | Ethics Committee |

| | |
|---|---|
| ECG | electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| EGFR | epidermal growth factor receptor |
| ESC | Executive Safety Committee |
| FACS | fluorescence-activated cell sorting |
| FDA | Food and Drug Administration |
| FSH | follicle-stimulating hormone |
| FXa | Factor Xa |
| GC/GEJC | gastric cancer and gastroesophageal junction cancer |
| GCP | Good Clinical Practice |
| GFR | glomerular filtration rate |
| GI | gastrointestinal |
| GLP | Good Laboratory Practice |
| GnRH | gonadotropin-releasing hormone |
| GU | genitourinary |
| HBsAg | Hepatitis B surface antigen |
| HCV | Hepatitis C virus |
| HCV Ab | Hepatitis C virus antibody |
| HIV | human immunodeficiency virus |
| HLH | hemophagocytic lymphohistiocytosis |
| HNSCC | head and neck squamous cell carcinoma |
| HR | hazard ratio |
| IC+ | percentage of tumor-associated immune cells with staining |
| ICF | informed consent form |
| ICH | International Conference on Harmonisation |
| ICI | Immune checkpoint inhibitor |
| ICP | Immune Cells Present |
| Ig | immunoglobulin |
| IHC | immunohistochemical |
| IMDC | International Metastatic RCC Database Consortium |
| INR | International Normalized Ratio |
| irAE | immune-related adverse event |
| IRB | Institutional Review Board |
| IRC | independent radiology committee |
| IRF | independent review facility |
| IRR | infusion-related reaction |
| IRT | Interactive Response Technology |
| irSAE | immune-related serious adverse events |
| ITT | intent-to-treat |

| | |
|---|---|
| IUD | intrauterine device |
| IUS | intrauterine hormone-releasing system |
| IV | intravenous |
| LEC | lower esophageal cancer |
| LDH | lactate dehydrogenase |
| LFT | liver function test |
| LH | luteinizing hormone |
| LMWH | low molecular weight heparins |
| MAS | macrophage activation syndrome |
| mCRC | metastatic colorectal cancer |
| mCRPC | metastatic castration-resistant prostate cancer |
| mCSPC | metastatic castration-sensitive prostate cancer |
| MDSC | myeloid-derived suppressor cell |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MHC | major histocompatibility complex |
| MI | myocardial infarction |
| MMR | mismatch repair |
| MRI | magnetic resonance imaging |
| MSI | microsatellite instability |
| MSKCC | Memorial Sloan-Kettering Cancer Center |
| MTC | medullary thyroid cancer |
| MTD | maximum tolerated dose |
| NA | Not applicable |
| NCI | National Cancer Institute |
| NE | not estimable |
| NHT | novel hormonal therapy |
| NR | Not reported |
| NSAID | Non-steroid 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 |
| PD | progressive disease |
| PD-1 | programmed death receptor 1 |
| PD-L1 | programmed death receptor 1 ligand |
| PE | pulmonary embolism |
| PFS | progression-free survival |
| PK | pharmacokinetic or pharmacokinetics |

| | |
|---|---|
| PO | by mouth |
| PPE | palmar-plantar erythrodysesthesia |
| PPI | proton pump inhibitor |
| PR | partial response |
| PSA | prostate-specific antigen |
| PSADT | prostate-specific antigen doubling time |
| PT | prothrombin time |
| PTT | partial thromboplastin time |
| qd | once daily |
| qod | every other day |
| QTcF | Corrected QT interval calculated by the Fridericia formula |
| RCC | renal cell carcinoma |
| RECIST (1.1) | Response Evaluation Criteria in Solid Tumors (version 1.1) |
| RPLS | reversible posterior leukoencephalopathy syndrome |
| RSI | reference safety information |
| RTK | receptor tyrosine kinase |
| SAA | Single-Agent Atezolizumab |
| SAC | Single-Agent Cabozantinib |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SD | stable disease |
| SI | Système Internationale |
| SLD | Sum of lesion diameter |
| SNP | single nucleotide polymorphism |
| SOC | Study Oversight Committee |
| SoD | Sum of the diameters |
| T3 | triiodothyronine |
| T4 | thyroxine |
| TAM | tumor-assisted macrophage |
| TBS | technetium bone scan |
| TIA | transient ischemic attack |
| TKI | tyrosine kinase inhibitor |
| TPR | time point response |
| $T_{reg}$ | regulatory T-cell |
| TSH | thyroid-stimulating hormone |
| UC | urothelial carcinoma |
| ULN | upper limit of normal |
| UPCR | urine protein/creatinine ratio |
| VAD | ventricular assist device |

| | |
|---|---|
| VEGF | vascular endothelial growth factor |
| VEGFR | vascular endothelial growth factor receptor |
| W#D# | Week # Day # |
| WBC | white blood cell |

# 1 BACKGROUND AND RATIONALE

## 1.1 Background

Multi-targeted tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs) immunotherapies represent two systemic modalities that have been instrumental in the recent advancements of anticancer treatment over the past several years. Both classes of therapies have demonstrated broad clinical effects leading to new approved treatment options across multiple tumor types. The success of these therapy types as single agents with distinct mechanisms of action has naturally led to interest in evaluating combinations of TKIs with ICIs in search of further, possibly synergistic, anticancer clinical effects.

### 1.1.1 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 in clinical activity across several tumor types.

Atezolizumab injection, for intravenous (IV) use (1200 mg once every 3 weeks [q3w]), has been approved in the 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 prescribing information [US PI] and European Medicines Agency Summary of Product Characteristics [EMA SmPC]). Recently, atezolizumab was also granted accelerated approval in the US for treatment in combination with paclitaxel protein-bound for adult patients with unresectable locally advanced or metastatic triple negative breast cancer (TNBC) whose tumors express PD-L1 (Schmid et al 2018) and was also approved for first-line treatment in combination with carboplatin and etoposide in adult patients with extensive-stage small cell lung cancer (ES-SCLC; Horn et al

2018, Tecentriq US PI). In these tumor indications, atezolizumab has either prolonged overall survival (OS) or induced durable disease responses. Notably, similar to other ICIs, the effects of single-agent atezolizumab on progression-free survival (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, and pancreatitis (Michot et al 2016; Tecentriq US PI and EMA SmPC).

#### 1.1.1.1 Clinical Experience in Urothelial Carcinoma

Regulatory approval of atezolizumab in locally advanced or metastatic UC was received based on results from a multicenter, open-label, Phase 2 study using objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors (version 1.1) (RECIST 1.1) by independent review facility (IRF) as primary endpoint, and based on the results from a randomized multicenter Phase 3 study comparing atezolizumab with standard of care chemotherapy in subjects previously treated with a platinum-based chemotherapy.

In cohort 2 of the Phase 2 study, which enrolled UC subjects who had received prior platinum-based chemotherapy, the overall ORR by IRF was 14.8% (95% confidence interval [CI]: 11.1, 19.3), for subjects with ≥ 5% PD-L1 expression 26.0% [95% CI: 17.7, 35.7], and for subjects with < 5% PD-L1 expression 9.5% [95% CI: 5.9, 14.3] (Rosenberg et al 2016; Tecentriq US PI). Median PFS for the overall population was 2.7 months (95% CI: 2.1, 4.2); subgroup analysis of PFS demonstrated longer median PFS in subjects with higher PD-L1 expression, with a median PFS of 4.1 months (95% CI: 2.3, 11.8) in subjects with ≥ 5% PD-L1 expression, 2.1 months (95% CI: 2.1, 5.4) in subjects with ≥ 1% and < 5% PD-L1 expression, and 2.6 months (95% CI: 2.1, 5.7) in subjects with < 1% PD-L1 expression. Median OS for the overall population was 15.9 months (95% CI: 10.4, not estimable [NE]); survival was shorter in subjects with ≥ 5% PD-L1 expression (12.3 months [95% CI: 6.0, NE]) compared with that of subjects with < 5% PD-L1 expression (19.1 months [95% CI: 9.8, NE]; Balar et al 2017). Atezolizumab was well-tolerated in this study population; the most frequently reported adverse events (AEs; ≥ 20% incidence) in descending order of frequency were fatigue, decreased appetite, diarrhea, nausea, anemia, pruritus, and increased blood creatinine. Adverse events led to treatment discontinuation in 8% of subjects. The most frequently reported irAE was rash (3%). Treatment-emergent anti-therapeutic antibodies were detected in 41.5% of subjects at one or more post-dose time points (Loriot et al 2016). However, the presence of these antibodies did not appear to have a clinically significant impact on pharmacokinetics (PK), safety or efficacy. In the

Phase 3 study, which also enrolled UC subjects after prior platinum-based chemotherapy, the results of atezolizumab were generally consistent with the Phase 2 study data. The overall ORR was 13% (95% CI: 11, 17) and for subjects with ≥ 5% PD-L1 expression 23.0% [95% CI: 16, 32]. The duration of response (DOR) in the overall population for the atezolizumab arm was 21.7 months compared with 7.4 months on the chemotherapy arm. Although the primary endpoint of OS in this study in the PD-L1 positive (≥ 5% expression level) was not met, there were numerical improvements in OS in the overall population (HR=0.85; 95% CI 0.73, 0.99) confirming the clinical benefit of atezolizumab in this patient population compared to standard of care chemotherapy. In addition, the safety profile of atezolizumab in this study was more favorable than for chemotherapy (Powles et al 2018).

In cohort 1 of the Phase 2 study, which enrolled treatment-naïve subjects with cisplatin-ineligible UC, the overall ORR by IRF was 23% (95% CI: 16, 31), for subjects with ≥ 5% PD-L1 expression 28% (95% CI: 14, 47), and for subjects with < 5% PD-L1 21% (Bellmunt et al 2016). The median OS for all subjects irrespective of PD-L1 expression level was 15.9 months (95% CI: 10.4, NE). The safety experience in treatment-naïve UC subjects was similar to subjects who had received prior platinum-based therapy.

A multi-center, randomized Phase 3 study evaluating atezolizumab as a single agent or in combination with platinum-based chemotherapy in subjects with treatment-naïve advanced UC (cisplatin-eligible and cisplatin-ineligible) is ongoing (NCT02807636). An interim analysis demonstrated that subjects with PD-L1 low status had decreased OS in the single-agent atezolizumab arm compared with chemotherapy alone. As a result, the study stopped enrolling subjects with PD-L1 low expression status to the single-agent atezolizumab arm. Based on these results, first-line approval for single-agent atezolizumab in advanced UC was restricted to subjects with PD-L1 expression on immune cells (IC) of ≥ 5% for those not eligible for cisplatin-containing therapy. In the US only, for subjects who are ineligible for any platinum-based agent, the approval status remained unconstrained by PD-L1 status.

#### 1.1.1.2 Clinical Experience in Renal Cell Carcinoma

Safety, tolerability, and preliminary clinical activity of single-agent atezolizumab in subjects with advanced renal cell carcinoma (RCC) of clear cell or non-clear cell histology was demonstrated in a Phase 1 study (McDermott et al 2016). Approximately 10% of subjects in this study had not received prior systemic treatment for RCC. The ORRs for clear cell RCC ranged from 9 to 18% depending on PD-L1 expression status. Overall median PFS and median OS for subjects with clear cell RCC were 5.6 months (95% CI: 3.9, 8.2) and 28.9 months (95% CI: 20.0, NE), respectively. One out of seven enrolled subjects with non-clear cell RCC experienced a

response per immune-related response criteria. Treatment-related Grade 3 events were reported for 17% of subjects, and there were no Grade 4 or 5 treatment-related AEs.

Atezolizumab has also demonstrated encouraging clinical activity in combination with the vascular endothelial growth factor (VEGF)-targeting antibody bevacizumab in a randomized Phase 2 study in treatment-naïve metastatic RCC (Atkins et al 2017). The ORR regardless of PD-L1 expression level was 32% and in PD-L1 positive subjects (≥ 1% PD-L1 expression) was 46%. Median PFS regardless of PD-L1 expression level was 11.7 months (95% CI: 8.4-17.3) and in PD-L1 positive subjects 14.7 months (95% CI: 8.2-25.1). The safety profile of this combination therapy was consistent with the safety profiles of the individual treatment components.

In a multicenter, randomized Phase 3 study, atezolizumab in combination with bevacizumab (Atezo+Bev) was compared with sunitinib as first-line therapy in advanced or metastatic RCC (Motzer et al 2018; Rini et al [Lancet] 2019; NCT02420821). The co-primary endpoints of the study were investigator-assessed PFS in PD-L1 positive tumors (≥1% expression on tumor-infiltrating immune cells) and overall survival in the ITT population. A total of 915 subjects were enrolled (ITT population); 362 subjects were defined as PD-L1 positive (178 in the Atezo+Bev arm, 184 in the sunitinib arm). The study met its co-primary endpoints. The Atezo+Bev arm showed statistically significant improved PFS for PD-L1 positive subjects compared with sunitinib (median PFS: 11.2 vs 7.7 months; HR: 0.74; 95% CI: 0.57, 0.96; p=0.02). Investigator-assessed PFS in the ITT population was also improved (11.2 vs 8.4 months). Median OS in the PD-L1 positive and ITT populations at the time of the primary PFS endpoint analysis and the second interim analysis (approximately 10 months after the first interim analysis) were not reached for the Atezo+Bev arm but showed an encouraging trend. In addition, there were fewer high-grade treatment related AEs in the Atezo+Bev arm compared to sunitinib control arm (Grade 3/4 AEs: 40% vs 54%) at the time of the primary PFS analysis.

A Phase 2 study evaluating atezolizumab in combination with bevacizumab in subjects with advanced RCC of non-clear cell histology is ongoing (NCT02724878).

#### 1.1.1.3 Clinical Experience in Non-Small Cell Lung Cancer

Regulatory approval of atezolizumab in platinum-pretreated NSCLC was received based on results from a multicenter, randomized Phase 3 study of atezolizumab compared with docetaxel (Rittmeyer et al 2017). Subjects received either atezolizumab (1200 mg) or docetaxel (75 mg/m$^2$) every 3 weeks. Coprimary endpoints were OS in the ITT population and PD-L1 positive population (≥ 1% PD-L1 expression). Overall survival was significantly improved with

atezolizumab compared with docetaxel in the ITT population (median OS: 13.8 vs 9.6 months; hazard ratio [HR]=0.73, p=0.0003) and the PD-L1 positive population (median OS: 15.7 vs 10.3 months; HR=0.74, p=0.0102). The ORR was similar for the treatment arms (14% for atezolizumab vs 13% for docetaxel) in the ITT population; however, median DOR was longer with atezolizumab (16.3 months vs 6.2 months). Fewer subjects discontinued treatment due to AE in the atezolizumab arm (8%) versus the docetaxel arm (19%). The most common AEs of any grade for subjects on the atezolizumab arm were fatigue (14%), nausea (9%), decreased appetite (9%), and asthenia (8%). Immune-related AEs reported with atezolizumab included pneumonitis (four subjects, all Grade 3), hepatitis (two subjects, both Grade 4), and colitis (two subjects, both Grade 2). Fewer subjects had treatment-related Grade 3 or 4 AEs with atezolizumab (15%) than with docetaxel (43%).

Encouraging clinical activity of atezolizumab as first-line therapy in advanced NSCLC was demonstrated in a multicenter Phase 2 study (Peters et al 2017). Enrollment was selected on the basis of PD-L1 expression (≥ 5%) on tumor cells or immune cells. In untreated NSCLC patients with PD-L1 expression of ≥ 50% on tumor cells or ≥10% on immune cells (PD-L1 high group) the ORR (31%) per IRF was comparable to standard of care chemotherapy in this treatment setting. Median OS (26.9 months) in the PD-L1 high group was longer compared with standard of care chemotherapy in this treatment setting. Median duration of response in the PD-L1 high group was ~10 months and median PFS was 5.4 months. Subgroup analyses supported the hypothesis that results in radiographic endpoints PFS and ORR were dependent on the PD-L1 expression status; however, the observed OS benefit deemed to be independent of the PD-L1 expression status. Treatment-related AEs of Grade 3 or 4 of atezolizumab monotherapy occurred in 9% of subjects. There was no treatment-related Grade 5 event. Adverse events leading to treatment discontinuation occurred in 7% of subjects and included Grade 3 or 4 pneumonitis (1%) and any grade pneumonia (1%).

In a randomized Phase 3 study of atezolizumab and chemotherapy with or without bevacizumab (Atezo/Chemo ± Bev) significant improvements in PFS and OS were demonstrated compared with chemotherapy in combination with bevacizumab (Chemo/Bev) (Socinski et al [J Clin Oncol] 2018). The study enrolled 1202 previously untreated subjects with advanced NSCLC of non-squamous cell histology. Chemotherapy consisted of carboplatin AUC 6 in combination with paclitaxel 200 mg/m$^2$. Co-primary endpoints were investigator-assessed PFS in the ITT wildtype (WT) population (EGFR/ALK negative) and in WT subjects with an tumor T-effector gene signature (Teff-high WT), and OS in the ITT-WT population. The combination of Atezo/Chemo + Bev demonstrated an improvement of the co-primary endpoint PFS compared

with Chemo/Bev (median PFS 8.3 months vs 6.8 months; HR 0.617 [95% CI: 0.517, 0.737; P < 0.0001]). A PFS benefit was also observed in subjects with EGFR and ALK genetic alterations, PD-L1-negative tumors, and liver metastases (Reck et al 2017). With a 13.5-month minimum follow-up, the combination of Atezo/Chemo + Bev also improved the co-primary endpoint OS compared with Chemo/Bev (median OS ITT-WT 19.2 vs 14.7 months; HR=0.78 [95% CI: 0.64,0.96; p=0.204]). In EGFR/ALK positive subjects (N=104), median OS was not reached for the Atezo/Chemo + Bev combination and was 17.5 months for the Chemo/Bev combination (HR=0.54). Grade 3/4 treatment-related AEs occurred in 43%, 57%, and 49% of subjects in the Atezo/Chemo + Bev arm, Atezo/Chemo arm, and Chemo/Bev arm, respectively. No new safety signals were observed (Socinski et al [J Clin Oncol] 2018). Based on the results from this study, FDA approved atezolizumab in combination with bevacizumab, paclitaxel, and carboplatin for the first-line treatment of patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations.

Multicenter, randomized Phase 3 trials in chemotherapy-naïve advanced NSCLC are evaluating atezolizumab alone or in combination with different standard of care chemotherapy regimens vs standard of care chemotherapy in non-squamous and squamous NSCLC (NCT02409342, NCT02409355, NCT02367781, NCT02367794).

#### 1.1.1.4 Clinical Experience in Castration-Resistant Prostate Cancer

A Phase 1a study of atezolizumab enrolled 15 subjects with metastatic castration-resistant prostate cancer (mCRPC) (Kim et al 2018; NCT01375842). Subjects had received prior enzalutamide and/or sipuleucel-T for metastatic CRPC. The majority (87%) of subjects had received ≥ 2 prior lines of therapy. With a median survival follow up of 15.8 months, the landmark 12-month OS rate was 55.6% and median OS was not reached. Median PFS was 3.4 months (95% CI 2.3, 5.7). One subject had a partial response per modified RECIST and 45% had stable disease per RECIST 1.1. Two subjects (13%) had a ≥ 50% decrease in prostate-specific antigen (PSA) from baseline. In addition, increased CD8 expression and expansion of T-cell clones were observed in the subject who had experienced a response per modified RECIST.

A multicenter, randomized Phase 3 trial of the combination of atezolizumab with enzalutamide after failure of an androgen synthesis inhibitor in CRPC is ongoing; results from this study are not yet available (NCT03016312).

#### 1.1.1.5 Clinical Experience in Triple Negative Breast Cancer

A Phase 1 study evaluated single-agent atezolizumab in 115 subjects with metastatic TNBC (Schmid et al 2017; NCT01375842). Subjects had been treated with a median of 7 prior systemic

therapies; 58% were being treated as third-line or higher. Across all subjects, ORR according to RECIST was 10% with an ORR of 13% in PD-L1 positive subjects (> 5% expression). ORR was 26% in subjects treated in the first-line setting and 11% for those in the second-line setting. The disease control rate (DCR; PR+SD) was 23% in all subjects. At a median follow up of 15.2 months, the median OS was 9.3 months. One-year OS was 41%. Among responders, the 2-3 year survival rate was 100%. Exploratory analysis suggested that higher response rates seemed to be associated with higher levels of tumor-infiltrating lymphocytes, higher levels of CD8 T cells, and, to a lesser extent, higher PD-L1 expression.

A Phase 1b trial of atezolizumab in combination with nab-paclitaxel included 32 subjects with metastatic TNBC (NCT01633970). In this study, the ORR was 42% (10 of 24 evaluable subjects). Responses occurred in patients whose tumors expressed PD-L1 and in those with little to no PD-L1 expression. The most common treatment-related AE was decreased neutrophil count (53% all grade; 41% Grade 3 or 4). No DLTs or treatment-related deaths occurred. Nab-paclitaxel did not affect atezolizumab-induced proliferation of circulating activated CD8+ T cells.

Two Phase 3 studies comparing atezolizumab in combination with standard of care chemotherapy versus standard of care chemotherapy in previously untreated metastatic TNBC are ongoing (NCT02425891, NCT03125902). In the IMpassion130 study (NCT02425891), patients with untreated metastatic TNBC were randomly assigned in a 1:1 ratio to receive atezolizumab plus nab-paclitaxel or placebo plus nab-paclitaxel. Patients continued the intervention until disease progression or an unacceptable level of toxic effects occurred. Each group included 451 patients (median follow-up: 12.9 months). In the ITT analysis, the median PFS was 7.2 months in the atezolizumab plus nab-paclitaxel group and 5.5 months in the placebo plus nab-paclitaxel group (HR for progression or death: 0.80; 95% CI: 0.69, 0.92; $p = 0.002$); among patients with PD-L1 positive tumors, the median PFS was 7.5 months and 5.0 months, respectively (HR: 0.62; 95% CI: 0.49, 0.78; $p < 0.001$). In the ITT analysis, the median overall survival was 21.3 months in the atezolizumab plus nab-paclitaxel group and 17.6 months in the placebo plus nab-paclitaxel group (HR for death: 0.84; 95% CI: 0.69, 1.02; $p = 0.08$); among patients with PD-L1 positive tumors, the median overall survival was 25.0 months and 15.5 months, respectively (HR: 0.62; 95% CI: 0.45, 0.86) (Schmid et al 2018). Based on the results from this study, atezolizumab was granted accelerated approval in the US for treatment in combination with paclitaxel protein-bound for adult patients with unresectable locally advanced or metastatic TNBC and whose tumors express PD-L1. Results of the IMpassion131 study

(NCT03125902) comparing atezolizumab in combination with paclitaxel versus placebo and paclitaxel are not yet available.

#### 1.1.1.6 Clinical Experience in Ovarian Cancer, Primary Peritoneal Cancer, and Fallopian Tube Cancer

In a Phase 1a dose escalation/expansion study (Infante et al 2016; NCT01375842), atezolizumab was evaluated in subjects with advanced ovarian cancer. Twelve subjects with a median age of 61 years were enrolled. The majority of subjects (11 of 12) had received at least 2 lines of prior anticancer therapy. Of nine response evaluable subjects, two achieved a PR (22%). One responding subject had an 8.1-month duration of response. Median PFS was 2.9 months (95% CI 1.3-5.5). Median OS was 11.3 months (95% CI 5.5-27.7) for all subjects and 17.4 months (95% CI 5.9-27.7) in nine subjects with an immune cell score of IC2/3. Responders to atezolizumab were IC2/3 and had low baseline CA125 levels.

Several Phase 3 studies of atezolizumab in combination with standard of care chemotherapy with or without bevacizumab in untreated and previously treated subjects with ovarian, fallopian tube, or primary peritoneal cancer are ongoing (NCT03353831, NCT02891824, NCT03038100).

#### 1.1.1.7 Clinical Experience in Endometrial Cancer

In a Phase 1a study, atezolizumab was evaluated in subjects with advanced or recurrent endometrial cancer (Fleming et al 2017; NCT01375842). Fifteen subjects were enrolled (5 endometrioid, 5 serous, 1 ER+ leiomyosarcoma, 4 unknown); median age was 61 years, 93% had $\geq$ 2 prior systemic therapies, and 67% had prior radiotherapy. The ORR was 13% (2 subjects both with IC2/3 immune cell score for PD-L1 expression). One responder was MS-Stable and heavily infiltrated with tumor-infiltrating lymphocytes (TILs; IC3, 70% TILs, unknown subtype); the other responder was hypermutated, MSI-High, and moderately infiltrated with TILs (IC2, 10% TILs, endometrioid). Duration of response for these subjects was 7.3 and 8.1+ months, respectively. Median PFS was 1.7 months (0.5-11+ months), and median OS was 9.6 months (0.6-11.8+ months). DCR (PR+SD) was 27%. There were no Grade 4 or 5 treatment-related AEs reported.

#### 1.1.1.8 Clinical Experience in Hepatocellular Carcinoma

In a Phase 1b study of atezolizumab (1200 mg q3w) in combination with the anti-VEGF targeting antibody bevacizumab, 103 subjects with advanced HCC naïve to systemic therapy had been enrolled at the data cutoff of 26 July 2018 (NCT02715531; Pishvaian et al 2018). Among 73 efficacy-evaluable subjects, the median survival follow-up was 7.2 months. The ORR by independent radiology facility (IRF) was 27% (with 4 complete responses [CRs]) per RECIST

1.1 and was 34% (with 8 CRs) per modified RECIST (mRECIST); ORR by the Investigator per RECIST 1.1 was 32% with 1 CR. Confirmed responses were reported across the patient population regardless of HCC etiology, geographic region, baseline alpha-fetoprotein (AFP) levels, or extrahepatic spread of tumor. The investigator-assessed median PFS per RECIST 1.1 was 14.9 months, and the IRF-assessed median PFS per RECIST 1.1 was 7.5 months. Median estimates for duration of response (DOR) and OS were not yet reached at the data cutoff of 26 July 2018. Among the 103 safety-evaluable subjects, treatment-related Grade 3 or 4 AEs were reported in 28 subjects (27%), most commonly hypertension (n = 10 [10%]). Five (5) Grade 5 AEs were observed, 2 of which were assessed as treatment related (one sepsis, one pneumonitis). A total of 19 subjects (18%) experienced treatment-related serious adverse events (SAEs). Adverse events of special interest (AESIs) of any grade for atezolizumab were reported for 54% of subjects, and AESIs of any grade for bevacizumab were reported for 47% of subjects. Immune-related AESIs for atezolizumab of ≥ Grade 3 requiring corticosteroid treatment included pneumonitis (2 subjects), autoimmune encephalitis, drug-induced liver injury (DILI), colitis, AST increased, γ-glutamyltranspeptidase (GGT) increased, diabetes mellitus, and pancreatitis (1 subject each). The high response rate observed suggested that the combination of atezolizumab with bevacizumab has synergistic activity in advanced HCC and compared favorably to early single-agent atezolizumab data in treatment-naïve HCC.

These results improved upon the preliminary single-agent data of atezolizumab in subjects with treatment-naïve advanced HCC, in which few objective responses were observed (the following data provided by Roche). Single-agent activity of atezolizumab in previously untreated advanced HCC has been explored in two single-arm Phase 1 studies. Study NCT01375842 enrolled five treatment-naïve HCC subjects; there were no responders per investigator assessment. In Study NCT02825940 (currently ongoing), there were two confirmed responses per Investigator assessment out of seven treatment-naïve subjects.

A Phase 3 study of atezolizumab in combination with bevacizumab compared with sorafenib in patients with untreated locally advanced or metastatic hepatocellular carcinoma is ongoing (NCT03434379).

#### 1.1.1.9 Clinical Experience in Gastric Cancer

In a Phase 1 first-in-human dose escalation study (Taieb et al 2018; NCT01375842), atezolizumab was evaluated in subjects advanced gastric cancer (GC). Six subjects with advanced GC were enrolled following at least 2 prior systemic anticancer treatments. The ORR among the six subjects was 17%.

A randomized Phase 2 study of atezolizumab + FLOT (5-FU, calciumfolinat, oxaliplatin, and docetaxel) vs. FLOT alone in patients with advanced GC/GEJC is currently on-going (NCT03421288).

#### 1.1.1.10 Clinical Experience in Colorectal Cancer

In a Phase 1b study (Hochster et al 2017; NCT01633970), atezolizumab was evaluated in subjects with metastatic CRC (mCRC) either in combination with bevacizumab (Atezo/Bev) or in combination with bevacizumab and a FOLFOX chemotherapy (Atezo/Bev/Chemo; Wallin et al 2016). Among 10 previously treated mCRC subjects defined as micro-satellite instability high (MSI-H), treatment with Atezo/Bev resulted in an ORR of 30% and a DCR (PR+SD) of 90%. Median duration of treatment was 10.2 months and median duration of response was 7.8 months (range: 5.5+ to 7.8 months). Median PFS was not estimable (range: 1.5+ to 18.3 months) and median OS was not reached at the date of the cutoff. Among 30 mCRC subjects treated with atezo/bev/chemo unconfirmed ORRs was 40% (Bendell et al 2015). In 23 first-line subjects who had 1 year of additional follow up, the ORR was 52%, the median duration of response was 11.4 months, and the median PFS was 14.1 months. The most common Grade 3 AEs across both arms were neutropenia (7%), increased AST (5%), increased ALT (2%), diarrhea (2%), fatigue (2%), and hypophosphatemia (2%). No Grade 4 or 5 AEs considered possibly related to study treatment were observed.

Two Phase 3 studies in subjects with deficient DNA mismatch repair CRC are ongoing with either atezolizumab alone or in combination with standard of care chemotherapy and bevacizumab (NCT02997228, NCT02912559).

#### 1.1.1.11 Clinical Experience in Head and Neck Cancer

In a Phase 1a study (Bahleda et al 2017; NCT01375842) atezolizumab was evaluated in subjects with recurrent and/or metastatic head and neck cancer. Of 32 enrolled subjects, 84% were male (median age of 62 years), 66% reported current or previous tobacco use, and all had been heavily pre-treated with 53% of patients receiving ≥ 2 prior lines of therapy. The most common primary tumor location was in the oropharynx (56%); other common primary tumor sites included the oral cavity (22%) and nasopharynx (13%). With a median follow up of ≥ 14 months, the ORR was 22%, median PFS was 2.6 months (range: 0.5 to 48.4 months), and median OS was 6.0 months (range: 0.5 to 51.6 months). Clinical activity was observed independent of PD-L1 IHC or HPV status.

A Phase 3 study of atezolizumab compared with placebo as adjuvant therapy in patients with high risk-locally advanced squamous cell carcinoma of the head and neck is ongoing (NCT03452137).

#### 1.1.1.12 Clinical Experience in Thyroid Cancer

A Phase 2 study (NCT03181100) of atezolizumab in unresectable or metastatic anaplastic thyroid cancer and poorly differentiated thyroid cancer is ongoing. Subjects receive an induction phase with Nab-paclitaxel or paclitaxel while waiting for their molecular testing result. Corresponding to their molecular status, subjects with BRAF mutation status will receive atezolizumab + vemurafenib + cobimetinib, subjects with RAS mutation status will receive atezolizumab + cobimetinib, and subjects without BRAF or RAS mutation will receive atezolizumab + bevacizumab.

### 1.2 Cabozantinib

Cabozantinib (XL184) is a potent inhibitor of multiple receptor tyrosine kinases (RTKs) known to play important roles in tumor cell proliferation and/or tumor neovascularization including MET, vascular endothelial growth factor receptor (VEGFR), AXL, and RET. Increased expression of MET and AXL has been implicated in the development of resistance to VEGFR inhibitors in preclinical models of several cancers (Shojaei et al 2010, Zhou et al 2016, Sennino et al 2012, Ciamporcero et al 2015). In addition, targets of cabozantinib are implicated in promoting tumor-immune suppression including TYRO3, MER, and AXL (tumor-assisted macrophage [TAM] family kinases). Cabozantinib has demonstrated broad preclinical and clinical activity across several tumor types including RCC, UC, CRPC, and NSCLC. In the US and the EU, cabozantinib capsules (140 mg) are approved for the treatment of progressive, metastatic medullary thyroid cancer (Elisei et al 2013; Cometriq™ US PI and EMA SmPC). Cabozantinib tablets (60 mg) are approved in the US for the treatment of patients with advanced RCC and in the EU for the treatment of advanced RCC after prior VEGFR-targeted therapy and for previously untreated advanced RCC of intermediate or poor risk (Choueiri et al 2015, Choueiri et al 2016, Choueiri et al [J Clin Oncol] 2017, Choueiri et al [Ann Oncol] 2017, Cabometyx™ US PI and EMA SmPC).

Summaries of cabozantinib pharmacology, toxicology, PK, and clinical data are contained in the Investigator's Brochure supplied by the Sponsor (or designee), which must be reviewed before initiating the study.

### 1.2.1 Nonclinical Toxicology

Cabozantinib nonclinical toxicology has been characterized in single- and repeat-dose studies in multiple species. Details can be found in the Investigator's Brochure.

### 1.2.2 Clinical Experience in Renal Cell Carcinoma

The cabozantinib approval in previously treated RCC was based on the results of a multicenter, randomized, controlled Phase 3 study comparing open-label cabozantinib (60 mg, tablets) with everolimus in 658 subjects (330 cabozantinib, 328 everolimus) with advanced disease and clear cell histology who had received prior therapy with at least one VEGFR-TKI (NCT01865747; Choueiri et al 2015, Choueiri et al 2016, Cabometyx US PI and EMA SmPC). Cabozantinib demonstrated statistically significant improvements in the primary endpoint (PFS) and both secondary endpoints (ORR, OS) compared with the standard-of-care in the control arm (everolimus). In the primary PFS analysis performed in the first 375 subjects randomized (Primary Endpoint Intent-to-Treat population), the HR per independent radiology committee (IRC) adjusted for stratification factors was 0.58 (95% CI: 0.45, 0.74; stratified log-rank p-value < 0.0001), and the Kaplan-Meier estimates for median duration of PFS were 7.4 months in the cabozantinib arm vs 3.8 months in the everolimus arm. In the primary analysis of ORR per IRC conducted in the intent-to-treat (ITT) population at the time of the primary analysis of PFS, the ORRs for the cabozantinib and everolimus arms, were 17% (95% CI: 13, 22) and 3% (95% CI: 2, 6), respectively (unstratified p-value <0.0001). In a subsequent unplanned interim OS analysis with a prospectively-defined cutoff date providing a minimum follow-up of 13 months from the last subject randomized, a highly statistically significant prolongation of OS for subjects in the cabozantinib arm compared with the everolimus arm was demonstrated: the HR, adjusted for stratification factors was 0.66 (95% CI: 0.53, 0.83; stratified log-rank p-value 0.0003). Kaplan-Meier estimates for median duration of OS were 21.4 months in the cabozantinib arm and 16.5 months in the everolimus arm. Results for extensive subgroup analyses of PFS, OS, and ORR showed a consistent benefit for cabozantinib treatment versus everolimus. The observed clinical activity of cabozantinib was applicable to subjects in all risk categories per Memorial Sloan-Kettering Cancer Center (MSKCC) criteria and was irrespective of previous treatments and the extent of tumor burden. Consistent with the known safety profile for cabozantinib, the most frequently reported AEs for subjects who received cabozantinib on study in decreasing order of frequency were diarrhea, fatigue, nausea, decreased appetite, palmar-plantar erythrodysesthesia (PPE), hypertension, vomiting, weight decreased, and constipation (Cabometyx US PI). Adverse events were generally adequately managed with dose modifications (reductions and interruptions) with dose reductions from 60 mg to 40 mg occurring in 60% of subjects and further dose reductions from 40 mg to 20 mg occurring in

20% of subjects. Treatment discontinuations due to AEs were similar between the two treatment arms (10% incidence in each arm), and the most frequent AEs leading to treatment discontinuation in the cabozantinib arm were decreased appetite and fatigue.

The cabozantinib approval for previously untreated RCC was based on results of a randomized, open-label Phase 2 trial (NCT01835158) comparing cabozantinib (60 mg) with sunitinib (50 mg) in 157 subjects (79 cabozantinib, 78 sunitinib) in treatment-naïve RCC with clear cell histology conducted as part of a collaboration with the National Cancer Institute's (NCI) Cancer Therapy Evaluation Program (CTEP; Choueiri et al [J Clin Oncol] 2017). The trial met its primary endpoint, demonstrating a statistically-significant and clinically-meaningful improvement in PFS for cabozantinib compared with sunitinib in previously untreated subjects with advanced RCC of intermediate- or poor-risk per International Metastatic RCC Database Consortium criteria. The median PFS per Investigator for the cabozantinib arm was 8.2 months (95% CI 6.2, 8.8) compared with 5.6 months (95% CI: 3.4, 8.1) on the sunitinib arm. Cabozantinib reduced the rate of disease progression or death by 34% compared with sunitinib (adjusted HR = 0.66; 95% CI: 0.46 to 0.95; Choueiri et al [J Clin Oncol] 2017). Median PFS per IRC for the cabozantinib arm was 8.6 months (95% CI 6.8, 14.0) compared with 5.3 months (95% CI: 3.0, 8.2) on the sunitinib arm (Choueiri et al [Ann Oncol] 2017). Median OS was 26.6 months on the cabozantinib arm and 21.2 months on the sunitinib arm (HR = 0.79; 95% CI: 0.53, 1.2; two-sided p=0.27). Adverse events of ≥ Grade 3 regardless of causality occurred in 68% of cabozantinib subjects and 65% of sunitinib subjects; these events included diarrhea (cabozantinib 10%, sunitinib 11%), fatigue (6%, 17%), hypertension (28%, 21%), PPE (8%, 4%), and hematological events (2%, 21%). In both study arms, 16 subjects (20% cabozantinib, 21% sunitinib) discontinued study treatment due to an AE. The safety data in the cabozantinib-treated arm of the study were consistent with those observed in previous studies in subjects with advanced RCC.

Cabozantinib has also been evaluated in subjects with advanced RCC of non-clear cell histology (Lemke et al 2018). In a retrospective study (N=68), the clinical outcome of subjects with non-clear cell histologies (eg, papillary, chromophobe, translocation, sarcomatoid de-differentiation) was compared with the outcome of subjects with clear cell histology. Analyzed subjects had received cabozantinib as first-line or later line therapy. The most common risk categories were intermediate and poor; other unfavorable prognostic markers such as bone and liver metastases were frequently present. Overall survival was similar in both study groups (median OS: non-clear cell histology 25.3 months, clear cell histology 20.5 months). The study demonstrated that cabozantinib has clinical activity in RCC across subtypes of non-clear cell

histology. Cabozantinib is recommended as a first-line therapy in subjects with advanced RCC of non-clear cell histology (NCCN [Kidney Cancer] 2019).

### 1.2.3 Clinical Experience in Urothelial Carcinoma

Cabozantinib (60 mg) has been evaluated as a single agent in an open-label Phase 2 study of subjects with relapsed or refractory metastatic UC (Apolo et al [J Clin Oncol] 2016; NCT01688999). A total of 67 eligible subjects with diagnoses of progressive metastatic carcinoma of the bladder, urethra, ureter, or renal pelvis were enrolled in three cohorts. The largest cohort (Cohort 1) enrolled 50 subjects with metastatic UC. In Cohort 1, the primary endpoint of ORR for 42 evaluable subjects was 19.1% with 7 PRs and 1 CR for single-agent cabozantinib. Median PFS and median OS for these subjects were 3.7 months (95% CI: 3.1, 6.5) and 8.0 months (95% CI: 5.2, 10.3), respectively. Across all cohorts (n=67), the most frequent (≥ 5% incidence) Grade 3 AEs related to cabozantinib treatment were fatigue (9%), hypertension (7%), and hypophosphatemia (6%). Cabozantinib-related Grade 4 AEs were reported for hypomagnesemia (3%) and lipase increased (1%).

In an ongoing Phase 1 clinical trial (Apolo et al [Ann Oncol] 2016, Nadal et al 2017; NCT02496208) in subjects with refractory metastatic UC and other genitourinary (GU) tumors, cabozantinib has been evaluated in combination with nivolumab, a monoclonal antibody to PD-1 (referred to as doublet), and in combination with nivolumab and ipilimumab, a monoclonal antibody targeting CTL4-A (referred to as triplet). The doublet and triplet combinations were well tolerated and no dose-limiting toxicities (DLTs) were reported (Apolo et al [Ann Oncol] 2016). The recommended phase 2 doses for the doublet combination were cabozantinib 40 mg daily (qd) with nivolumab 3 mg/kg IV every other week (q2w), and for the triplet combination cabozantinib 40 mg qd with nivolumab 3 mg/kg IV q2w and ipilimumab 1 mg/kg IV every third week (q3w; maximum 4 doses). At the data cutoff, 42 subjects across both the doublet and triplet combinations were evaluable for safety and response analyses. The ORR across all subjects with heavily pre-treated GU tumors was 33% (Nadal et al 2017). Among the metastatic UC subjects, a 38% ORR was reported with 15% achieving a CR. Also, subjects with rare UC types such as urachal adenocarcinoma and squamous cell carcinoma of the bladder responded to this combination therapy. After a median follow up of 16 months, median DOR was not reached with approximately 70% ongoing responses; the median OS was 20 months among enrolled GU cancers. Grade 3 or 4 treatment-related AEs across all different dose levels explored for the doublet combination (n=24 subjects) were fatigue (12%), hypertension (8%), diarrhea (4%), nausea or vomiting (4%), abdominal pain (4%), thromboembolic events (4%), and kidney infection (4%). Most frequent Grade 3 or 4 treatment-related AEs across all different dose levels

explored for the triplet combination (n=18 subjects) were fatigue (11%), hypertension (17%), diarrhea (5%), anorexia (5%), oral mucositis or sore throat (5%), thromboembolic events (5%). Immune-related Grade 3 or Grade 4 AEs on the doublet combination arm comprised one case of aseptic meningitis, and on the triplet combination arm one event of colitis and hepatitis each. Grade 3 or 4 laboratory abnormalities reported in ≥ 2 subjects on the doublet arm across all explored dose levels were decreased neutrophil count (n=6), hypophosphatemia (n=5), increased lipase (n=4), decreased platelet count (n=2), hyponatremia (n=2), and proteinuria (n=2). Grade 3 or 4 laboratory abnormalities reported in ≥ 2 subjects on the triplet arm across all explored dose levels were hypophosphatemia (n=4), increased lipase (n=4), decreased lymphocyte count (n=3), hyponatremia (n=2), hypocalcemia (n=2), alanine aminotransferase (ALT) increased (n=2, both Grade 3), AST increased (n=1, Grade 3), and amylase increased (n=1). There was no Grade 5 AE. In an additional Expansion Cohort, subjects refractory to prior ICI therapy were treated with the combination of cabozantinib and nivolumab. Among seven subjects refractory to prior ICI therapy, two subjects had PRs (29%) with a median duration of response of 5.6 months, and four subjects had SD as their best response (57%). The clinical benefit rate (PR + SD) in this cohort was 86% (Nadal et al 2018).

### 1.2.4 Clinical Experience in Castration-Resistant Prostate Cancer

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, comparator 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 novel hormonal therapy (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; HR = 0.90 [95% CI: 0.76 to 1.06; stratified log-rank p = 0.21]) nor PSA outcomes compared with prednisone. Improvement in median radiographic PFS was observed in the cabozantinib group (5.6 vs 2.8 months; HR = 0.48 [95% CI: 0.40 to 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 treatment may be futile, and to differences in post-progression therapies (eg, cabazitaxel). Grade 3 to 4 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 patients with late line disease. It is worth noting that this trial enrolled patients in third or later line mCRPC where no therapy has yet proved efficacious; nevertheless, there was a trend (albeit statistically non-significant) in OS favoring cabozantinib in addition to the positive findings on PFS favoring cabozantinib. Furthermore, an OS benefit among patients who received cabozantinib was observed in a posthoc subgroup analysis of those with visceral disease enrolled in COMET-1. Of 191 patients (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 to 0.92; p = 0.018]).

Additional encouraging preliminary results in CRPC subjects have been observed in the ongoing Phase 1 study combining cabozantinib with nivolumab (+/- ipilimumab). One of nine enrolled subjects with metastatic CRPC (11%) experienced a PR, and 67% had stable disease as their best response (Nadal et al 2017; NCT02496208). These results warrant further evaluation of the combination of cabozantinib with ICIs in CRPC.

### 1.2.5 Clinical Experience in Non-Small Cell Lung Cancer

Cabozantinib has been evaluated as a single agent or in combination in several early stage clinical trials in patients with advanced NSCLC.

In an open-label, randomized Phase 2 study, 125 NSCLC subjects without EGFR genetic alterations received cabozantinib, erlotinib, or both agents in combination as second or third line treatment (Neal et al 2016; NCT01708954). Compared with erlotinib alone, the primary endpoint PFS was significantly improved in subjects receiving cabozantinib as a single agent (4.3 vs 1.8 months; HR=0.39, p=0.0003) and in combination with erlotinib (4.7 vs 1.8 months; HR=0.37, p=0.0003). The estimated median OS for cabozantinib treated subjects was 9.2 months (95% CI: 5.1, 15.0), for cabozantinib with erlotinib was 13.3 months (95% CI 7.6, NR), and for erlotinib alone was 5.1 months (95% CI 3.3-9.3). The ORR for subjects treated with cabozantinib alone was 11%, with the combination of cabozantinib with erlotinib was 3%, and with erlotinib alone was 3%. Notably, progression as best response was reported for 66% of subjects treated with erlotinib alone compared with 23-24% for subjects treated with cabozantinib alone or in combination with erlotinib. The most common Grade 3 or 4 AEs for single-agent cabozantinib were hypertension (25%), fatigue (15%), oral mucositis (10%), diarrhea (8%), and

thromboembolic event (8%). One death due to respiratory failure assessed as possibly related to study drug occurred in the cabozantinib arm, and one death due to pneumonitis assessed as related to either study drug or the combination occurred in the erlotinib plus cabozantinib arm.

In a Phase 2 randomized discontinuation trial (RDT) of cabozantinib, 60 subjects with advanced NSCLC were enrolled (Schöffski et al 2017; NCT00940225). The ORR was 10%, and 48.3% of subjects experienced stable disease as their best response. Median PFS in this study was 4.0 months.

In a Phase 2 trial of cabozantinib, 26 subjects with advanced RET-rearranged NSCLC were enrolled (Drilon et al 2016; NCT01639508). The study met its primary endpoint, with an ORR of 28% (95% CI 12, 49). The median duration of treatment was 4.7 months. The median PFS was 5.5 months (95% CI: 3.8, 8.4). The median OS was 9.9 months (95% CI 8.1, not reached). The most common Grade 3 treatment-related AEs were lipase elevation (15%), increased ALT (8%), increased AST (8%), decreased platelet count (8%), and hypophosphatemia (8%).

### 1.2.6 Clinical Experience in Triple Negative Breast Cancer

In a Phase 2 study of cabozantinib, 35 subjects with metastatic TNBC were enrolled (Tolaney et al 2017; NCT01738438). Median age was 50 years, and subjects received up to 3 prior lines of chemotherapy. The ORR was 9% (95% CI: 2, 26) with three partial responses. Twenty of 35 subjects (57%) had SD as their best response which lasted over 15 weeks in 9 of 35 subjects (26%). Changes in circulating cell populations were evaluated by flow cytometry. A persistent increase of circulating CD3+ cells and a persistent decrease of CD14+ monocytes were observed possibly reflecting activation of systemic antitumor immunity. The most common AEs were fatigue, diarrhea, oral mucositis, hand and foot syndrome, anorexia, elevated AST and ALT, hypertension, nausea, and dysgeusia. A total of 15 Grade 3 events were reported including two cases of elevated AST, three cases of elevated lipase, and two cases of hypertension. No Grade 4 events were reported.

### 1.2.7 Clinical Experience in Ovarian Cancer, Primary Peritoneal Cancer, and Fallopian Tube Cancer

In a randomized discontinuation Phase 2 trial (RDT) of cabozantinib, 70 subjects with advance ovarian cancer were enrolled (Vergote et al 2017; NCT00940225). Median age was 61 years; 93% had the ovary as primary disease site and 7% had the peritoneum as the primary disease site. The most common histologic subtypes were serous, endometrioid, and clear cell. Half of the subjects were platinum-refractory or resistant, and the majority of subjects had received ≥ 2 prior lines of therapy including prior platinum-based chemotherapy. The primary endpoint of ORR at

week 12 was 21% (14 subjects) with one subject achieving a CR. The overall DCR (CR+PR+SD) at Week 12 was 50%; 70% of subjects with at least one post-baseline tumor assessment had tumor regression. Median PFS for all subjects was 5.5 months (2.8 months in subjects with platinum-refractory/resistant disease and 6.9 months for subjects with platinum-sensitive disease). Twenty-two of 62 subjects (35%) with baseline CA125 values greater than the upper limit of normal had CA125 responses (defined as > 50% reduction from baseline). The most common ≥ Grade 3 AEs were diarrhea (14%), PPE, hypertension, and neutropenia (each 6%). Due to frequent peritoneal disease manifestation, GI perforations and/or fistulas are common. In this study, four subjects experienced GI perforations and/or fistulas (two of which were fatal). Overall, the safety profile was consistent to that observed with other anti-angiogenic agents in subjects with ovarian cancer.

In an additional open-label, Phase 2 study, 111 subjects with recurrent ovarian cancer were 1:1 randomized to receive either cabozantinib or paclitaxel (Matulonis et al 2016; NCT01716715). Subjects were allowed to have received up to three prior therapy regimens. Response for cabozantinib-treated subjects was 8.3% and for paclitaxel-treated subjects 28.3%. Median OS was 19.4 months in the cabozantinib arm versus not reached in the paclitaxel arm.

### 1.2.8 Clinical Experience in Endometrial Cancer

In a Phase 2 study of cabozantinib, 102 subjects were enrolled with endometrial cancer recurring within one year of adjuvant chemotherapy or with progression after 1 line of chemotherapy for metastatic disease (Dhani et al 2017; Mandilaras et al 2017; NCT01935934). Histologic subtypes included endometrioid and serous (each 36 subjects) and a poor prognosis cohort of clear cell carcinosarcoma (30 subjects). In 32 evaluable subjects with endometrioid histology, the ORR was 19% and median PFS was 4.8 months (95% CI: 4.4, 6.4 months). In 29 subjects with serous histology, the ORR was 14% with a median PFS of 4.2 months (95% CI: 2.7, 5.0 months). In 15 evaluable subjects with carcinosarcoma, the ORR was 7% and median PFS was 3 months (95% CI: 2.7, 4.6 months). The most frequent Grade 3/4 AE was hypertension. There were no new safety signals identified.

### 1.2.9 Clinical Experience in Hepatocellular Carcinoma

The clinical activity and safety of single-agent cabozantinib (60 mg, tablets) in HCC has been demonstrated in a randomized placebo-controlled Phase 3 study (CELESTIAL) in subjects who had received prior therapy with sorafenib (subjects were required to have progressed during or following prior systemic therapy and up to 2 prior lines of systemic therapy were allowed; Abou-Alfa et al 2018). The primary endpoint of the study was OS. At the second pre-planned interim analysis, the prespecified event-driven primary efficacy endpoint analysis of the

707 subjects enrolled at the data cutoff (470 cabozantinib, 237 placebo) demonstrated a statistically significant improvement in OS for subjects in the cabozantinib arm compared with placebo (Intent-to-Treat [ITT] population): the HR, adjusted for stratification factors, was 0.76 (95% CI: 0.63, 0.92; stratified log-rank p-value = 0.0049; critical p-value to reject the null hypothesis of equal OS = 0.021). The Kaplan-Meier estimates for median duration of OS were 10.2 months in the cabozantinib arm vs 8.0 months in the placebo arm. The secondary endpoint analysis of PFS as determined by the investigator yielded a median duration of PFS of 5.2 months in the cabozantinib arm and 1.9 months in the placebo arm. The HR, adjusted for stratification factors, was 0.44 (95% CI: 0.36, 0.52, stratified log-rank p-value < 0.0001). Investigator-determined objective response rate (ORR) was 4% and 0.4% for subjects in the cabozantinib and placebo arms, respectively (unstratified Fisher exact test p-value = 0.0059); all were partial responses (PRs). In addition, there was a high rate of stable disease (SD) in the cabozantinib arm relative to placebo (60% vs 33%). Adverse events reported for ≥ 20% of subjects in the cabozantinib arm by decreasing frequency were diarrhea, decreased appetite, palmar-plantar erythrodysesthesia (PPE), fatigue, nausea, hypertension, vomiting, aspartate aminotransferase (AST) increased, and asthenia. Grade 3 or 4 adverse events (AEs) regardless of causality were reported for 68% of subjects in the cabozantinib arm and 36% in the placebo arm. Grade 3 or 4 AEs reported for ≥ 5% of subjects in the cabozantinib arm by decreasing frequency were PPE, hypertension, AST increased, fatigue, diarrhea, asthenia, and decreased appetite Based on the results of this study in subjects who had received prior sorafenib, cabozantinib tablets (60 mg) as a single agent have been approved in the US, EU, and other regions for an HCC indication (Cabometyx US PI and EMA SmPC).

In a Phase 2 randomized discontinuation trial (RDT; NCT00940225; Kelley et al 2017), 41 subjects with advanced HCC were enrolled. Key eligibility criteria included up to 1 line of prior systemic therapy, documented progression of disease, and Child-Pugh score of A. Median age was 60 years, and most subjects were male. Thirty-seven percent of subjects were of Asian ancestry. The most frequent cause of HCC was cirrhosis (44%), unknown (29%), HBV (24%), HCV (24%), and alcohol-related (20%). The majority of subjects (80%) had received prior systemic therapy; 54% had received sorafenib. Extrahepatic spread was present in 73% of subjects. Among 37 evaluable subjects, three had a confirmed PR. Seventy-eight percent had at least one tumor assessment which demonstrated a reduction in measurable disease. Of the 26 subjects with elevated baseline alpha-fetoprotein (AFP) and ≥ 1 post-baseline measurement, 9 (35%) had AFP response (> 50% reduction from baseline). Progression-free survival was 5.2 months, and OS was 11.5 months. The most common Grade 3/4 AEs, regardless of causality, were diarrhea (20%), PPE (15%), and thrombocytopenia (15%).

### 1.2.10 Clinical Experience in Gastric Cancer

In a Phase 1 study of cabozantinib, four subjects with advanced gastric cancer (GC) or gastroesophageal junction cancer (GEJC) were enrolled (Kurzrock et al 2011; NCT00215605). One subject with GEJC had a decrease in the sum of tumor measurements of approximately 20% from baseline.

In a Phase 2 randomized discontinuation trial (RDT) of cabozantinib, 21 subjects with advanced GC or GEJC were enrolled (Schöffski et al 2017; NCT00940225). Subjects were allowed to have received up to one prior systemic anticancer treatment. The primary endpoint ORR in the GC/GEJC cohort was 4.8% with 1 confirmed PR; there were also 8 subjects with SD as best response. The DCR (PR + SD) at Week 12 for the GC/GEJC cohort was 33% (95% CI: 14.6, 55.1). The safety results in the RDT study with cabozantinib were consistent with those for patients with advanced cancer treated with other VEGFR-TKIs.

### 1.2.11 Clinical Experience in Colorectal Cancer

In a Phase 1 study of cabozantinib, eight subjects with mCRC were enrolled (Kurzrock et al 2011; NCT00215605). The colon was the primary tumor site in five subjects, and the rectum was the primary tumor site in three subjects. A total of four of the eight subjects had a decrease in the sum of tumor target lesions.

In a Phase 1b study of cabozantinib in combination with panitumumab, 18 subjects with KRAS WT mCRC were enrolled (Strickler et al 2016; NCT02008383). Subjects received 60 mg cabozantinib in combination with panitumumab 6 mg/kg q2w. A majority of subjects had an ECOG performance status of 1 and had received ≥ 5 prior treatments including EGFR-targeted therapy. The ORR was 13% with a median PFS of 3.7 months and a median OS of 7.5 months. The most common Grade 3 treatment-related AEs were diarrhea (17%), rash, and oral mucositis (each 11%). There were no Grade 4 or Grade 5 treatment-related AEs.

### 1.2.12 Clinical Experience in Head and Neck Cancer

A Phase 2 study of cabozantinib with an immune checkpoint inhibitor in subjects with head and neck squamous cell carcinoma who have failed platinum based therapy is ongoing (NCT03468218).

### 1.2.13 Clinical Experience in Differentiated Thyroid Cancer

In a Phase 1 drug-drug interaction study of cabozantinib, 15 subjects with radioactive-iodine (RAI)-refractory DTC that was metastatic or unresectable were enrolled (Cabanillas et al 2014; NCT01100619). Histologic subtypes included 7 subjects (47%) with papillary thyroid

cancer (PTC), 5 subjects (33%) with follicular thyroid cancer (FTC), and 3 subjects (20%) with Hürthle cell carcinoma (HTC). Median age was 53 years. Subjects had received up to ≥ 4 systemic therapies, and three subjects were treatment-naïve. The majority of subjects (73%) had received prior VEGFR-targeted therapy. Of the 14 subjects evaluable for tumor response, 8 subjects (53%) had a confirmed PR and 6 subjects (40%) had stable disease (SD), four of whom had SD lasting ≥ 6 months. Tumor regression appeared independent of prior VEGFR-targeted therapy. The DCR (CR + PR + SD) at Week 17 was 80%. Among the eight subjects with an objective response, including those with censored data, duration of response ranged from 61 to 442 days; the median duration of response (DOR) was not reached. At a median follow-up of 12.2 months (range: 10.3 to 17.0), the median PFS was not reached. At a median follow-up of 25.8 months (range: 23.9 to 30.7), the median OS was also not reached. Diarrhea (20%) and hypertension (13%) were the most frequently reported Grade 3 AEs.

In a Phase 2 study of cabozantinib, 25 subjects with RAI-refractory DTC that had progressed after prior VEGFR-targeted therapy were enrolled (Cabanillas et al 2017; NCT01811212). Disease histologies included PTC (36%), poorly differentiated thyroid cancer (28%), HTC (20%), and FTC (16%). Subjects had a high tumor burden, and were heavily pre-treated with systemic cytotoxic chemotherapy and/or targeted therapies including VEGR-targeted agents (seven subjects had received ≥ 2 lines of treatment, three had received three lines of treatment, and one had received four lines of treatment). Distant metastases at study entry included bone for 84% of subjects, liver for 36%, and brain for 20%. Of the 23 subjects evaluable for tumor response, 10 subjects (40%) had a confirmed PR, and 13 subjects (52%) had SD; objective responses were observed across all histologic types and in subjects who had brain metastases at study entry. A total of 10 of 21 subjects who had received only 1 prior VEGFR-targeted therapy achieved a response. The median PFS was 12.7 months (95% CI: 10.9, 34.7), and the median OS was 34.7 months (95% CI: 18.3, not reached). The most frequent Grade 3 AEs (≥ 5%) were fatigue (12%), weight loss (12%), diarrhea, and PPE (each 8%). The safety profile was similar to that of other VEGFR-targeted therapies in DTC subjects.

In a Phase 2 study of cabozantinib, 35 subjects with RAI-refractory thyroid cancer who were treatment naïve to VEGFR inhibitors were enrolled (Brose et al 2018; NCT02041260). Median age was 65 years. Disease histologies included PTC (66%), HTC (9%), and poorly differentiated (26%). The ORR was 54%, and the SD rate 43%. Nine subjects (26%) experienced SD for greater than 6 months. Seventeen subjects had a best target lesion reduction of ≥ 30%, and the disease control rate (CR+PR+SD > 6 months) was 80%. As of 06 February 2018, 16 subjects still remained on treatment. Although median PFS had not been reached (6 subjects

had experienced PD), PFS at 6 months and 12 months were 88% and 65%, respectively. Adverse events of ≥ Grade 3 severity occurring in more than 1 subject were hypertension (14%), increased lipase (9%), pulmonary embolism (PE, 6%), and hyponatremia (6%).

### 1.2.14 Immunological Effects

Cabozantinib is a potent inhibitor of multiple RTKs known to play important roles in tumor cell proliferation and/or tumor neovascularization including MET, VEGFR, and RET. In addition, targets of cabozantinib are implicated in promoting tumor immune suppression including TYRO3, MER, and AXL (TAM family kinases). Through preclinical and preliminary clinical evaluation, cabozantinib treatment has been shown to affect tumor cells and the tumor microenvironment in a manner that would potentially make them more sensitive to immune-mediated attack. In vitro and in vivo experiments employing a murine colon carcinoma cell line (MC38-CEA) demonstrated that cabozantinib treatment altered immune modulation and immune subset conditioning (Kwilas et al 2014). Specifically, treatment of tumor cells with cabozantinib in vitro led to increased tumor-cell expression of major histocompatibility complex (MHC) class 1 antigen and greater sensitivity of tumor cells to T-cell-mediated killing. In a mouse MC38-CEA tumor model, cabozantinib treatment led to increased peripheral CD8+ T-cell counts, decreased regulatory T-cells ($T_{reg}$s) and myeloid-derived suppressor cells (MDSCs), and decreased $T_{reg}$ suppressor activity. Further, synergistic effects including increased CD8+ T-cell infiltration and decreased infiltration by MDSCs and TAMs were observed when a poxviral-based cancer vaccine was administered in addition to cabozantinib in the mouse tumor model.

In the clinical setting, reductions in immunosuppressive $T_{reg}$ lymphocytes following treatment with cabozantinib were observed in the Phase 2 study of subjects with advanced refractory UC discussed in Section 1.2.3 (Apolo et al 2014). In a Phase 2 study in metastatic triple-negative breast cancer, cabozantinib-treated subjects experienced a persistent increase in the fraction of circulating CD3+ T lymphocytes and a persistent decrease in the CD14+ monocytes possibly reflecting activation of systemic antitumor immunity (Tolaney et al 2016).

Together, the preclinical and clinical observations presented above suggest that cabozantinib promotes an immunopermissive environment which might present an opportunity for synergistic effects from combination treatment with PD-1 checkpoint inhibitors.

## 1.3 Rationale

### 1.3.1 Rationale for the Study and Study Design

**Rationale for Treatment Combination**: Through potent inhibition of RTKs including MET, VEGFR, and RET, cabozantinib has demonstrated clinical activity as a single agent across multiple tumor types (see Section 1.2). In addition, targets of cabozantinib are implicated in promoting tumor-immune suppression including TYRO3, MER, AXL (TAM family kinases). Preclinical studies (Kwilas et al 2014, Song et al 2015, Lu et al 2017) and clinical observations on circulating immune suppressive cells and immune effector cells (Apolo et al [J Clin Oncol] 2014) suggest that cabozantinib promotes an immune-permissive environment which might present an opportunity for synergistic effects from combination treatment with ICIs which may be independent of tumor PD-L1 expression. Atezolizumab, a potent PD-L1 inhibitor that has also demonstrated clinical activity in multiple tumor types (see Section 1.1.1) is an appropriate combination therapy for this evaluation.

**Rationale for Dose-Escalation Stage**: In the Dose-Escalation Stage of the study, an appropriate cabozantinib dose and treatment schedule for the combination of cabozantinib with the standard dosing regimen of atezolizumab will be established in subjects with advanced UC or RCC. This will be achieved through the implementation of a traditional “3 plus 3” dose-escalation study design evaluating three possible cabozantinib dose levels and two possible treatment schedules.

At the time of Protocol Amendment 2.0 the recommended dose and dosing schedule for the Expansion Stage had already been identified (combination treatment of 40 mg cabozantinib qd orally plus 1200 mg atezolizumab q3w IV using the Standard Dosing Schedule).

**Rationale for Evaluating Selected Tumor Types**: In the Expansion Stage, 20 tumor-specific cohorts in RCC, UC, CRPC, NSCLC, TNBC, OC, EC, HCC, GC/GEJC/LEC, CRC, H&N, and DTC will be enrolled to receive the combination treatment in order to further evaluate the safety and efficacy in these tumor indications on the recommended dose and schedule. The rationale for the planned Expansion Cohorts is based on available clinical activity and safety of both drugs in these solid tumors as monotherapy or in combination therapies (see Section 1.2 [cabozantinib] and Section 1.1.1 [atezolizumab]).

In addition to exploring cabozantinib in combination with atezolizumab in subjects who had already received standard of care anticancer therapy, Expansion Cohorts 1, 3, 4, 10, 14, and 18 will include subjects with advanced cancer who have not received prior systemic anticancer therapy for inoperable locally advanced or metastatic cancer. This is supported by the observed

clinical activity of cabozantinib and/or ICIs including atezolizumab in previously untreated subjects as well as the evolving treatment landscape in advanced solid tumors.

**Rationale for Expansion Cohorts 1 and 10 (RCC)**: In Expansion Cohort 1 subjects with advanced untreated RCC with clear cell histology will be evaluated. Current treatment guidelines for patients with advanced RCC of clear cell histology include single VEGFR-targeted agents, combination therapy with a PD-1 and a CTL4-Ag directed ICI, or a PD-1 directed ICI with VEGFR-targeted therapy (NCCN [Kidney Cancer] 2019). Cabozantinib tablets (60 mg) are approved in the US as a single agent for the treatment of patients with advanced RCC and in the EU for the treatment of advanced RCC after prior VEGFR-targeted therapy and for previously untreated advanced RCC of intermediate or poor risk (Choueiri et al 2015, Choueiri et al 2016, Choueiri et al [J Clin Oncol] 2017, Choueiri et al [Ann Oncol] 2017, Cabometyx US PI and EMA SmPC). In addition, the PD-1 inhibitor nivolumab has been approved in combination with ipilimumab (a CTLA-4 antagonist) by demonstrating improved OS compared with sunitinib in untreated RCC patients of intermediate- and poor-prognosis (Opdivo [nivolumab] SmPC; Escudier et al 2017; NCT02231749).

Recently, two Phase 3 studies evaluating a PD-1 targeting ICI in combination with a VEGFR targeting TKI met their primary endpoint(s):

- In the open-label KEYNOTE-426 study (Rini et al [N Engl J Med] 2019; NCT02853331), 861 patients with previously untreated advanced clear-cell RCC were randomly assigned 1:1 to receive pembrolizumab plus axitinib or sunitinib monotherapy. After a median follow-up of 12.8 months, the 12-month survival rate was 89.9% with pembrolizumab plus axitinib vs 78.3% with sunitinib (HR = 0.53); median PFS was 15.1 months vs 11.1 months (HR = 0.69); and the ORR was 59.3% vs 35.7%. The benefit of pembrolizumab plus axitinib was observed irrespective of risk groups or PD-L1 status. Grade 3 or higher AEs occurred in 75.8% of patients in the pembrolizumab–axitinib group and in 70.6% in the sunitinib group.

- In the JAVELIN Renal 101 study (Motzer et al, 2019; NCT02684006), 886 patients with previously untreated advanced RCC were randomly assigned 1:1 to receive avelumab plus axitinib or sunitinib monotherapy. Among the 560 patients with PD-L1 positive tumors, the median PFS was 13.8 months with avelumab plus axitinib vs 7.2 months with sunitinib (HR = 0.61), and the ORR was 55.2% vs 25.5%. At a median follow-up for OS of 11.6 months and 10.7 months in the two treatment groups, 37 patients and 44 patients had died, respectively. In the overall population, the median PFS was 13.8 months with avelumab

plus axitinib vs 8.4 months with sunitinib (HR = 0.69). Grade 3 or higher AEs occurred in 71.2% of patients in the avelumab plus axitinib group and 71.5% in the sunitinib group.

Based on these Phase 3 results both combination therapies were approved in the US for the first-line treatment of patients with advanced RCC.

In addition, atezolizumab in combination with the VEGF-targeting antibody bevacizumab met its primary endpoint in a Phase 3 study (NCT02420821, IMmotion151) by improving investigator-assessed PFS in PD-L1 positive (≥ 1% expression) untreated advanced RCC compared to standard of care therapy sunitinib (Motzer et al 2018; NCT01984242). Several other Phase 3 studies of ICIs in combination with agents targeting CTLA-4 or in combination with VEGF(R)-targeted therapy are ongoing (NCT02684006; NCT02811861; NCT03141177). These clinical observations hold promise for clinical activity of the combination of cabozantinib and atezolizumab in subjects with advanced untreated RCC of clear histology.

In Expansion Cohort 10 subjects with advanced treatment-naïve or pretreated RCC of non-clear cell histology will be evaluated. Non-clear cell RCC is a heterogeneous patient population and includes a variety of histological subtypes including but not limited to papillary, chromophobe, collecting duct, and sarcomatoid. Current treatment guidelines for patients with advanced RCC with clear cell histology include VEGFR-targeted agents including cabozantinib as initial systemic anticancer therapy (NCCN [Kidney Cancer] 2019). Besides targeting the VEGF-signaling pathway, a critical component of tumor growth and invasion, there is a biologic rationale for using cabozantinib in non-clear cell RCC with genetic alterations of the MET oncogene (eg, papillary non-clear cell RCC). In a retrospective study, cabozantinib demonstrated encouraging single agent clinical activity in non-clear cell advanced RCC comparable to clear cell histology (Lemke et al 2018). In addition, emerging clinical data support the use of ICIs in non-clear cell RCC (Brandao Moreira et al 2017). The biologic rationale is based on findings that PD-L1 expressing non-clear cell RCC tumors appear to have worse clinical outcomes (Choueiri et al 2014).

**Rationale for Expansion Cohorts 2, 3, 4, 5 (UC)**: Combination chemotherapy regimens are the standard of care in first-line advanced urothelial carcinoma. Cisplatin-based chemotherapy is currently standard of care first-line treatment unless the subject is deemed cisplatin unfit (ie, cisplatin ineligible) due to ECOG status ≥ 2, creatinine clearance (CrCl) < 60 mL/min, ≥ Grade 2 hearing loss, or ≥ Grade 2 neuropathy (Milowsky et al 2016; Witjes et al 2017). In the second-line setting, single-agent chemotherapy is the standard of care and includes taxanes (docetaxel, paclitaxel) or vinflunine. More recently ICIs have demonstrated encouraging activity

in advanced UC (Davarpanah et al 2017, Hanna et al 2017). Both PD-1 and PD-L1 targeting ICIs have been approved as single agents following progression on platinum-based chemotherapy on the basis of improved clinical activity and good tolerability when compared to single-agent chemotherapy. The ICIs atezolizumab and pembrolizumab have also received accelerated approval status as first-line single-agent therapy for cisplatin unfit patients on the basis of response rate and duration of response in early stage clinical studies. Recently, in ongoing first-line Phase 3 studies both atezolizumab and pembrolizumab showed an unfavorable survival outcome compared to chemotherapy for cisplatin-ineligible subjects with PD-L1 low expressing tumors. As a result, enrollment of subjects with PD-L1 low expressing tumors was discontinued in the single-agent experimental arms of these studies. The experimental arms with a combination of ICI therapy and chemotherapy were not affected. The US PI was updated to allow atezolizumab for UC subjects who are not eligible for cisplatin-containing chemotherapy and whose tumors express a certain level of PD-L1, and for UC subjects who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status (Tecentriq US PI).

Despite the recent advances in the treatment of advanced UC, there is an unmet need in the cisplatin-fit (ie, cisplatin eligible) and unfit populations as well as in subjects previously treated with platinum-based therapy. The majority of patients with advanced UC are older than 65 years. The treatment of elderly patients with chemotherapy is challenging due to the presence of comorbid conditions. Following first line therapy median survival is approximately 10-15 months and 5-year survival rate is less than 20% (Sternberg et al 2006; von der Maase et al 2000; von der Maase et al 2005). Immune checkpoint inhibitors have become a new treatment option to manage advanced UC and represent a significant development for this disease. However, not all subjects with advanced UC benefit from these novel therapies. In order to improve the efficacy of ICIs, combination therapy approaches are being actively investigated (NCT02807636, NCT02853305, NCT02516241, NCT03036098).

Cabozantinib has demonstrated single-agent activity in previously treated subjects with advanced UC (Apolo et al [J Clin Oncol] 2016). Further, the combination of cabozantinib with a PD-1 targeting ICI demonstrated improved clinical activity compared to single agent use of either agent in subjects with advanced UC (Nadal et al 2017). The observed clinical activity and tolerability of the combination therapy holds promise for the combination therapy of cabozantinib with atezolizumab in subjects with advanced UC in the first-line and later-line settings.

In Expansion Cohort 2 of this study, subjects with advanced UC who have progressed on or after prior standard of care platinum-based chemotherapy (single agent or combination therapy) are

allowed to be enrolled. In Expansion Cohort 3 previously untreated subjects for advanced UC who are unfit for cisplatin-based chemotherapy are allowed to be enrolled. In Expansion Cohort 4, previously untreated subjects with advanced UC who are fit for cisplatin-based therapy are allowed to be enrolled.

For Expansion Cohort 5, subjects with advanced UC who previously progressed on ICI therapy are allowed to be enrolled. The objective of Cohort 5 is to evaluate the potential of cabozantinib with its immuno-permissive effects to re-sensitize to ICI therapy in order to prolong duration of response and survival. There is a high unmet need to overcome resistance to ICI therapy in cancer patients. In a recent study, resistance to prior ICI therapy could be reversed by cabozantinib in combination with nivolumab in patients with advanced UC (Nadal et al 2018).

**Rationale for Expansion Cohorts 6, 23, and 24 (mCRPC)**: In Expansion Cohort 6, subjects with castration-resistant prostate cancer (mCRPC) who have previously received enzalutamide and/or abiraterone acetate and experienced radiographic disease progression in soft-tissue will be enrolled. Prostate cancer patients who progress on androgen-deprivation therapy have a poor prognosis. At this stage of disease, standard treatment options include anti-androgen therapy (eg, enzalutamide, abiraterone), chemotherapy (eg, docetaxel, cabazitaxel), and radionuclides (eg, radium 223). There is emerging evidence that certain types of immunotherapy may provide clinical benefits to patients with advanced prostate cancer. For example, sipuleucel T, a cancer vaccine, has been approved for minimally symptomatic metastatic CRPC (Kantoff et al 2010). Recently, ICIs have been evaluated as potential new treatment modality for patients with CRPC. For example, the PD-1 inhibitor pembrolizumab has shown preliminary clinical activity in CRPC patients following progression on enzalutamide, an anti-androgen agent, with normalization of PSA, radiographic responses, and resolution of cancer pain (Graff et al 2016). A possible explanation of the observed clinical activity is based on the observation of upregulated PD-L1 expression upon exposure to enzalutamide (Bishop et al 2015). These data suggest that the likelihood of a response to immunotherapy in CRPC may be improved after progression on enzalutamide therapy. In addition, targeting immune suppressive cells has been suggested as a treatment strategy to further augment anti-tumor immune response in patients with prostate cancer. For example, MET inhibition has been shown to impede neutrophil recruitment to tumors and lymph nodes and this activity potentiates T cell anti-tumor immunity (Glodde et al 2017). 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). Also, high levels of circulating 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 (Treg) have been identified in patients with prostate cancer and may hamper the anti-tumor response (Miller et al 2006). Combined therapy of cabozantinib and ICIs were demonstrated to be potentially relevant in a preclinical CRPC model, where the combination induced a robust response in both primary and metastatic sites by reducing the immunosuppressive activity of MDSC in the tumor microenvironment (Lu et al 2017). The collective preclinical evidence supports the combination of cabozantinib with atezolizumab as a therapeutic strategy for CRPC. In addition, both cabozantinib and atezolizumab have shown clinical activity as single agents in previously treated patients with mCRPC (Smith et al 2016, Kim et al 2018).

In this Phase 1b study, the combination of cabozantinib with atezolizumab has been evaluated in the initially enrolled Cohort 6 subjects with mCRPC and measurable disease (n=66 as of 12 November 2019). The combination therapy appears to be well tolerated with a safety profile similar to what has been observed for single-agent therapy with cabozantinib or atezolizumab. Preliminary efficacy results are very encouraging and clinically meaningful with durable partial and complete responses and PSA decreases in particular in CRPC subjects with “high-risk” clinical features defined as the presence of visceral metastasis and/or extrapelvic lymph node metastasis. The clinical activity observed for 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 suggesting synergistic effects of these agents (Schöffski et al. 2017, Kim et al 2018). Based on encouraging preliminary efficacy data of the combination therapy, the protocol was amended to add two mCRPC cohorts to evaluate the efficacy of the combination treatment in high-risk CRPC subjects with measurable visceral disease or extrapelvic lymph nodes as follows:

- Expansion Cohort 23 (Cabozantinib 40 mg + Atezolizumab 1200 mg) will evaluate the combination therapy in high-risk mCRPC subjects who have progressed on or after one novel hormonal therapy (NHT) but who have not received docetaxel for mCRPC.

- Subjects with mCRPC who have relapsed post-taxane-based chemotherapy treatment in mCRPC have a high unmet need with very limited treatment options and dismal prognosis. Expansion Cohort 24 will evaluate the combination therapy in high-risk mCRPC subjects who have progressed on or after at least one NHT and have received taxane-based chemotherapy for mCRPC.

**Rationale for Expansion Cohorts 7, 8, 9 (NSCLC)**: Platinum-based combination chemotherapy (eg, cisplatin/pemetrexed) is a standard of care for subjects with Stage IV NSCLC without an actionable genetic alteration. Subsequent therapy may include single-agent chemotherapy (eg, pemetrexed, docetaxel). More recently, ICIs, either as single agents or in combination with chemotherapy, have demonstrated improved treatment outcomes for subjects with advanced NSCLC. Current treatment guidelines include single-agent pembrolizumab as first-line therapy in NSCLC subjects with high PD-L1 expression (tumor proportion score ≥ 50%) (Reck et al 2016; Hanna et al 2017). Pembrolizumab as a single agent in untreated NSCLC has also demonstrated clinical activity in subjects with PD-L1 expression scores of 1% or more (Lopes et al 2018). Single-agent ICIs including atezolizumab are also approved as a treatment alternative to single-agent chemotherapy in subjects with advanced NSCLC following progression on platinum-containing chemotherapy. For NSCLC subjects with sensitizing EGFR mutations, targeted therapy with EGFR-TKIs is the standard of care prior to receiving chemotherapy-based therapy (NCCN [NSCLC] 2018).

Cabozantinib has demonstrated single-agent activity in unselected, previously treated NSCLC subjects with results comparable to second line standard of care chemotherapy (Neal et al 2016; Schöffski et al 2017). Encouraging single-agent activity of cabozantinib has also been demonstrated in untreated and pretreated NSCLC subjects with RET-rearrangement (Drilon et al 2016). Atezolizumab has been approved in chemotherapy-pretreated NSCLC based on improving OS compared with docetaxel (Rittmeyer et al 2017; Tecentriq™ US PI and EMA SmPC). Clinically meaningful activity of atezolizumab single agent was also demonstrated in unselected untreated NSCLC subjects. For example, OS for atezolizumab-treated patients compared favorably to historical data with combination chemotherapy (23.5 months with atezolizumab vs 10-12 months with platinum-based chemotherapy). Objective response rate in untreated and pretreated NSCLC subjects was dependent of PD-L1 status (Peters et al 2017). In subjects with high PD-L1 expression (≥ 50% on tumor cells or ≥ 10% on immune cells) the ORR per independent review was 31% (range: 20%, 43%), which is comparable to chemotherapy in this patient population. Recently, the combination of atezolizumab with chemotherapy and bevacizumab demonstrated a statistically significant improvement in the co-primary endpoints of PFS and OS compared with chemotherapy and bevacizumab (Socinski et al [NEJM] 2018). Based on the results from this study, FDA approved atezolizumab in combination with bevacizumab, paclitaxel, and carboplatin for the first-line treatment of patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations.

Preliminary results in subjects with GU cancers suggest that combined therapy of cabozantinib with ICIs may reveal synergistic effects with greater clinical benefit (Nadal et al ESMO 2017). These clinical observations hold promise for clinical activity of the combination therapy of cabozantinib with atezolizumab in NSCLC subjects. In Cohort 7, subjects who have progressed on prior immune checkpoint inhibitor therapy will be enrolled. The objective of Cohort 7 is to evaluate the potential of cabozantinib with its immunopermissive effects to re-sensitize immune checkpoint inhibitor therapy in order to prolong duration of response and survival. In a recent NSCLC study resistance to prior immune checkpoint inhibitor therapy could be reversed by a VEGFR-TKI that has a target profile similar to cabozantinib in combination with an immune checkpoint inhibitor (Leal et al 2017). In Expansion Cohort 8, subjects with advanced Stage IV non-squamous NSCLC with PD-L1 tumor proportion score ≥ 50% and without a tumor genetic alteration (EGFR, ALK, ROS1, BRAF V600E) who have not received prior systemic anticancer therapy for metastatic disease will be enrolled. Atezolizumab and other ICIs such as pembrolizumab have demonstrated clinically meaningful single-agent activity in this patient population (Peters et al 2017, Reck et al 2016, Hanna et al 2017). It is anticipated that the combination of cabozantinib with atezolizumab may improve the clinical activity over single-agent use of atezolizumab in this patient population. In Expansion Cohort 9, subjects with advanced Stage IV non-squamous NSCLC with a sensitizing EGFR mutation who have progressed during or following prior treatment with at least one EGFR targeting TKI (eg, osimertinib, erlotinib, gefitinib, afatinib) will be enrolled. Subjects are allowed to have received standard of care therapy. Acquired resistance to EGFR-targeted therapy is a major unmet need in subjects with sensitizing EGFR mutations even for third-generation irreversible EGFR inhibitors (eg, osimertinib). An important mechanism of acquired resistance to EGFR TKI therapy is MET amplification which makes cabozantinib an attractive treatment strategy in this disease setting (Engelman et al 2007). The treatment landscape of EGFR mutant NSCLC has changed with the adoption of Atezolizumab + bevacizumab + platinum doublet chemotherapy. Starting with Protocol Amendment 4.0, this cohort began to allow subjects who have received prior ICI therapy for NSCLC subjects with sensitizing EGFR mutation. However, majority of the subjects relapse following targeted therapy. Relapse post targeted therapy for this population represents a high unmet need. MET amplification is a recognized mechanism of resistance following EGFR targeted therapy, and MET is a known target of cabozantinib. The potential of cabozantinib to create an immune permissive environment which synergizes with ICIs is a potential new treatment strategy for subjects harboring activating EGFR mutations after acquiring resistance to prior targeted TKI therapy.

**Rationale for Expansion Cohort 11 (TNBC)**: In Expansion Cohort 11, subjects with advanced triple-negative breast cancer (TNBC) who have progressed during or following treatment with at least one prior systemic anticancer therapy for inoperable locally advanced, or recurrent, or metastatic disease will be enrolled. TNBC accounts for about 15% of all breast cancers and is associated with a poor prognosis due to frequent visceral metastases. Standard of care therapy is systemic chemotherapy with agents such as anthracyclines, taxanes, anti-metabolites, microtubule inhibitors poly (ADP-ribose) polymerase inhibitors (PARP inhibitors) as well as other targeted therapies (NCCN [Breast Cancer] 2018). MET expression is increased in TNBC and is associated with poorer prognosis (Zagouri et al 2013). In addition MET copy number was found to be increased in TNBC (Gonzalez-Angulo et al 2013). These observations suggest that inhibition of MET signaling by cabozantinib may be a promising treatment strategy for TNBC. Encouraging clinical data of single agent cabozantinib therapy is available from heavily pretreated TNBC subjects (Tolaney et al 2017). TNBC may also be an optimal target for immune-based therapy due to its high rate of mutations and its high levels of programmed cell death ligand 1 (PD-L1) expression and tumor-infiltrating lymphocyte invasion. Emerging clinical data suggests that ICI therapies including atezolizumab may be an effective treatment strategy for TNBC (Schmid et al 2017; NCT01375842). In the IMpassion130 study (NCT02425891), patients with untreated metastatic TNBC were randomly assigned in a 1:1 ratio to receive atezolizumab plus nab-paclitaxel or placebo plus nab-paclitaxel. Patients continued the intervention until disease progression or an unacceptable level of toxic effects occurred. Each group included 451 patients (median follow-up: 12.9 months). In the ITT analysis, the median PFS was 7.2 months with atezolizumab plus nab-paclitaxel, as compared with 5.5 months with placebo plus nab-paclitaxel (hazard ratio for progression or death: 0.80; 95% CI: 0.69, 0.92; $p = 0.002$); among patients with PD-L1 positive tumors, the median PFS was 7.5 months and 5.0 months, respectively (hazard ratio: 0.62; 95% CI: 0.49, 0.78; $p < 0.001$). In the ITT analysis, the median overall survival was 21.3 months with atezolizumab plus nab-paclitaxel and 17.6 months with placebo plus nab-paclitaxel (hazard ratio for death: 0.84; 95% CI: 0.69, 1.02; $p = 0.08$); among patients with PD-L1 positive tumors, the median overall survival was 25.0 months and 15.5 months, respectively (hazard ratio: 0.62; 95% CI: 0.45, 0.86). No new adverse effects were identified. Adverse events that led to the discontinuation of any agent occurred in 15.9% of the patients who received atezolizumab plus nab-paclitaxel and in 8.2% of those who received placebo plus nab-paclitaxel (Schmid et al 2018). Based on the results from this study, atezolizumab was granted accelerated approval in the US for treatment in combination with paclitaxel protein-bound for adult patients with unresectable locally advanced or metastatic TNBC and whose tumors express PD-L1. With the approval of atezolizumab in combination with nab-paclitaxel in TNBC in the US, ICIs are now being used as frontline treatment for

patients with advanced TNBC who express PD-L1. Given that cabozantinib inhibits the MET signaling pathway and promotes an immunopermissive environment, combination with atezolizumab is a potential new therapeutic strategy in advanced TNBC. Starting with Protocol Amendment 4.0, this cohort began to allow TNBC subjects who have previously been treated with ICIs.

**Rationale for Expansion Cohort 12 (OC)**: In Expansion Cohort 12, subjects with advanced epithelial ovarian cancer (including primary peritoneal cancer or fallopian tube cancer), with platinum-refractory or resistant disease will be enrolled. Two prior lines of systemic anticancer therapies will be allowed including standard of care chemotherapy. Epithelial ovarian cancer is an aggressive malignancy. Despite optimal surgery and first-line carboplatin-taxane based combination chemotherapy, approximately 80% of subjects will develop a recurrence of disease. Subjects relapsing during first-line platinum-based chemotherapy (platinum-refractory) or within a few months after the completion this chemotherapy regimen (platinum-resistant) have an unfavorable prognosis. Standard of care therapy for recurrent platinum-resistant ovarian cancer is single-agent chemotherapy (paclitaxel, pegylated liposomal doxorubicin, or topotecan) which has modest clinical activity with ORRs of 10%–20%; median PFS of 3–4 months, and OS of approximately 12 months (NCCN [Ovarian Cancer] 2018). More recently, several PARP inhibitors have been approved for subjects with germline BRCA-mutated OC after prior chemotherapy or as maintenance therapy for subjects who responded to chemotherapy for recurrent OC (eg, olaparib, rucaparib, niraparib). The importance of targeting the VEGF-signaling pathway in ovarian cancer was demonstrated by adding bevacizumab to single-agent chemotherapy which improved PFS (Poveda et al 2015). There is a high unmet medical need to improve the clinical outcomes for subjects with recurrent platinum-refractory/resistant epithelial ovarian cancer. High PD-L1 expression of ovarian cancer cells has been associated with reduced infiltration of cytotoxic T lymphocytes into tumor and poorer clinical outcomes (Hamanishi et al 2007). Therefore, new strategies in recurrent epithelial ovarian cancer include the use of PD-1/PD-L1 targeting immune checkpoint inhibitors. Both cabozantinib and atezolizumab have demonstrated single agent activity in heavily pretreated epithelial ovarian cancer (Vergote et al 2017; Infante et al 2016). Therefore, the combination of cabozantinib with atezolizumab may represent new therapeutic options for patients with advanced ovarian cancer.

**Rationale for Expansion Cohort 13 (EC)**: In Expansion Cohort 13, subjects with advanced endometrial cancer (serous or endometrioid histology) who have progressed during or following treatment with at least one prior systemic anticancer therapy regimen will be enrolled. Standard

of care first-line therapy for recurrent or metastatic endometrial cancer includes platinum-based combination chemotherapy (usually carboplatin and paclitaxel) or single-agent chemotherapy (NCCN [Uterine Neoplasm] 2018). Novel therapies are needed for subjects who experience disease progression following standard of care first-line chemotherapy. Due to high expression levels of PD-L1 in primary and metastatic endometrial cancer, targeting the PD-1/PD-L1 signaling pathway with ICIs has become of interest (Vanderstraeten et al 2014). Both cabozantinib and atezolizumab have shown single agent activity in pretreated endometrial cancer subjects. Therefore, the combination of cabozantinib and atezolizumab represents a potential new treatment opportunity for subjects with recurrent or metastatic endometrial cancer (Dhani et al 2017; Fleming et al 2017).

**Rationale for Expansion Cohort 14 (HCC)**: In Expansion Cohort 14, subjects with advanced HCC (Child-Pugh A) who have not received prior systemic anticancer therapy will be enrolled. First-line therapy with single-agent VEGFR-TKIs has improved the outcome of subjects with advanced HCC; however, the survival benefit is modest with a median OS between 10.7 and 13.6 months (Llovet et al 2008; Kudo et al 2017). Both, cabozantinib and ICIs have shown promising single-agent clinical activity in advanced HCC (Abou-Alfa et al 2018; El-Khoueiry et al 2017). Based on the results from a randomized placebo-controlled Phase 3 study (CELESTIAL, NCT01908426) in subjects previously treated with sorafenib, cabozantinib tablets (60 mg) as a single agent have also been approved in the US, EU, and other regions for an HCC indication (Cabometyx US PI and EMA SmPC). Results of an ongoing clinical trial combining atezolizumab with bevacizumab suggest that a combination of ICI therapy with VEGF-targeting agents has synergistic clinical activity (Stein et al. ASCO 2018). Therefore, further evaluation of cabozantinib in combination with atezolizumab in previously untreated subjects with advanced HCC is warranted.

**Rationale for Expansion Cohort 15 (GC/GEJC/LEC)**: In Expansion Cohort 15, subjects with advanced gastric cancer, gastroesophageal junction cancer, or lower esophageal cancer (GC/GEJC/LEC) who have received standard of care first-line therapy systemic anticancer therapy including platinum or fluoropyrimidine-containing chemotherapy and Her-2/neu targeted therapy if indicated will be enrolled. Since lower esophageal cancer is biologically similar to GEJC (both are adenocarcinomas) and is treated similarly, they began to be included in this cohort starting with Protocol Amendment 4.0. Current available therapies for GC/GEJC/LEC generally do not provide durable responses, hence survival remains relatively short. Therefore, novel therapies with the potential to extend treatment response are needed. Cabozantinib and atezolizumab have shown preliminary single-agent activity in advanced GC/GEJC and may have

the potential for synergist effects when used in combination as salvage therapy in subjects with advanced GC/GEJC/LEC (Schöffski et al 2017; Taieb et al 2018).

**Rationale for Expansion Cohort 16 (CRC)**: In Expansion Cohort 16, subjects with advanced colorectal cancer (CRC) after progression on standard of care combination chemotherapy will be enrolled. Agents targeting the VEGF signaling pathway, including cabozantinib, have demonstrated clinical benefit in subjects with advanced or metastatic colorectal cancer (Grothey et al 2013; Strickler et al 2016). Immune checkpoint inhibitors including atezolizumab have demonstrated their clinical activity predominantly in patients whose tumors were defined as microsatellite instability-high (MSI-High, Hochster et al 2017). This condition is associated with an increased mutational burden and immune cell infiltration, making these subjects ideal candidates for treatment with ICIs. However, the majority of subjects with advanced colorectal cancer are MSI-Stable or MSI-Low. A possible strategy to increase the likelihood to respond to ICI therapy is through combination with agents that are able to change the tumor microenvironment (ie, by reducing the number of immune suppressive cells and increasing the number of immune effector cells). Preclinical and clinical studies have demonstrated that cabozantinib can induce an immune permissive environment which warrants the combination with atezolizumab in subjects with advanced or metastatic CRC.

**Rationale for Expansion Cohort 17 (H&N)**: In Expansion Cohort 17, subjects with advanced head and neck cancer of squamous cell histology after progression on standard of care systemic chemotherapy with or without EGFR-targeted therapy for recurrent, unresectable or metastatic disease will be enrolled. Following progression on first-line platinum-based chemotherapy there is no standard of care for second-line or third-line therapy. Treatment options in second-line include combination or single-agent chemotherapy, ICI or EGFR-targeted therapy (NCCN [Head and Neck Cancers] 2018). Elevated MET expression has been associated with poor prognosis in subjects with metastatic head and neck cancer of squamous cell histology (Madoz-Gurpide et al 2015). MET-pathway inhibition has also been demonstrated to overcome resistance to EGFR-targeted therapy in preclinical models (Krumbach et al 2011). Therefore, using drugs such as cabozantinib, which targets the MET-receptor, may be a potential new treatment option for subjects with advanced head and neck cancer. In addition, atezolizumab has demonstrated encouraging preliminary clinical activity in subject with recurrent/metastatic head and neck cancer independent of PD-L1 IHC or HPV status (Bahleda et al 2017). Recently pembrolizumab, either alone or in combination with platinum-based chemotherapy improved survival as first-line therapy for subjects with advanced H&N cancer of squamous cell histology (Burtness B et al, ESMO 2018). Based on these results, pembrolizumab as a single agent or in

combination with chemotherapy has been approved in the US for the treatment of advanced head and neck squamous cell cancer. The potential of cabozantinib to create an immune permissive environment which synergizes with ICIs is a potential new treatment strategy after acquiring resistance to ICI. Protocol Amendment 4.0 began to allow subjects with advanced H&N cancer who have received prior ICI therapy.

**Rationale for Expansion Cohort 18 (DTC)**: In Expansion Cohort 18, subjects with differentiated thyroid cancer (follicular, papillary, or poorly differentiated) refractory or deemed ineligible for radioactive iodine therapy (RAI) will be enrolled. VEGFR-targeting agents are standard of care first-line therapies in RAI-refractory DTC (NCCN [Thyroid Carcinoma] 2017). Cabozantinib has demonstrated very encouraging clinical activity in first-line RAI-refractory DTC and following prior VEGFR-targeting therapy (Brose et al 2018, Cabanillas et al 2014, Cabanillas et al 2017). In addition, advanced stages of thyroid cancer show high levels of PD-L1 expression which supports the use of ICIs in this tumor indication (Ahn et al 2017).

**Rationale for Exploratory Single-Agent Cabozantinib (SAC) Cohorts 19 (UC), 20 (NSCLC), and 21 (mCRPC)**: Cabozantinib has demonstrated single-agent activity in previously treated subjects with advanced UC (Apolo et al [J Clin Oncol] 2016). Cabozantinib has also demonstrated single-agent activity in unselected, previously treated NSCLC subjects with results comparable to second line standard of care chemotherapy (Neal et al 2016; Schöffski et al 2017). In addition, encouraging single-agent activity of cabozantinib has been demonstrated in untreated and pretreated NSCLC subjects with RET-rearrangement (Drilon et al 2016). Furthermore, cabozantinib has demonstrated improvement in PFS compared with prednisone in mCRPC subjects previously treated with docetaxel and NHT in COMET-1 study (Smith et al 2016; NCT01605227). Though OS benefit was not statistically significant, in a posthoc analysis of 191 patients with visceral metastases (133 cabozantinib, 58 placebo), the median OS was 7.1 months for those patients randomized to cabozantinib compared with 4.8 months for those on prednisone (stratified HR = 0.63 [95%CI: 0.44 to 0.92; p = 0.018]).

In this ongoing XL184-021 study, encouraging preliminary clinical activity has been observed in subjects who had high-risk features associated with mCRPC (ie, presence of measurable visceral metastasis or measurable extrapelvic lymphadenopathy) in Combination-Therapy Expansion Cohort 6. As of 12 November 2019, 66 CRPC subjects had been enrolled in this cohort, and clinically meaningful and durable partial and complete responses as well as PSA decreases had been observed in particular in CRPC subjects with high-risk clinical features. To further characterize the individual contribution of cabozantinib to the combination therapy in high-risk

mCRPC population, a single-agent cabozantinib cohort (SAC Cohort 21) to enroll the high risk CRPC patient population as in Expansion Cohort 23 was added to the study.

In summary, SAC Cohorts 19, 20, and 21 will further explore cabozantinib in subjects with advanced UC, NSCLC, and CRPC (same entry criteria as Combination-Therapy Expansion Cohorts 5, 7, and 23, respectively) to determine the individual contribution of cabozantinib to the clinical activity of the combination therapy. In order to provide subjects in these cohorts with the opportunity to receive combination therapy, a Second Agent Add-On Stage has been included in which subjects who radiographically progress on single-agent cabozantinib per RECIST 1.1 and meet combination-treatment eligibility requirements at that time may have atezolizumab added to their treatment regimen.

**Rationale for Exploratory Single-Agent Atezolizumab (SAA) Cohort 22 (mCRPC):**

There are limited data available on the clinical activity of atezolizumab in previously treated mCRPC (Section 1.1.1.4). The effect of atezolizumab in the high-risk CRPC population prior to receiving docetaxel in the mCRPC setting (ie, Expansion Cohorts 21-23 under study) is unknown. Therefore, the inclusion of a single-agent atezolizumab (SAA) cohort in this study will allow determination of the individual contribution of atezolizumab to the effects of the combination therapy with cabozantinib in subjects with high-risk mCRPC not treated with docetaxel in the castration-resistant setting. In order to provide subjects in this cohort with the opportunity to receive combination therapy, a Second Agent Add-On Stage has been included in which subjects who radiographically progress on single-agent atezolizumab per RECIST 1.1 and meet combination-treatment eligibility requirements at that time may have cabozantinib added to their treatment regimen.

### 1.3.2 Rationale for Dosage Selection and Treatment Schedule

In accordance with the US PI, atezolizumab will be administered at the standard dosing regimen of 1200 mg as an IV infusion over 60 min (± 15 min) every 3 weeks (-2 days) on Day 1 of each 21-day cycle (not applicable to Exploratory SAC Cohorts).

In the Dose-Escalation Stage, cabozantinib was to be administered orally at dose levels of 20, 40, or 60 mg in escalation cohorts. Sixty (60) mg is the approved tablet dose level for the single-agent treatment of advanced RCC and was also the dose used for the evaluation of cabozantinib as a single agent in the Phase 3 study in previously treated HCC and multiple Phase 2 studies in refractory metastatic UC, NSCLC, DTC, and CRPC. Dose reductions to 40 mg and 20 mg are utilized to manage AEs. In the Phase 3 METEOR study in RCC, the

average daily dose was 41 mg/day, taking into account dose modifications. The Dose-Escalation Stage was initiated at the 40 mg cabozantinib dose level. This dose was also the recommended dose determined for cabozantinib for the clinical evaluation in combination with nivolumab, another antibody inhibitor of the PD-1/PD-L1 pathway (Apolo et al [Ann Oncol] 2016). The Dose-Escalation Stage cohorts used the Standard Dosing schedule where cabozantinib and atezolizumab were started on Day 1 of Cycle 1.

On 22 February 2018, the Cohort Review Committee reviewed safety data of nine RCC subjects enrolled in the Dose-Escalation Stage: six RCC subjects at Dose Level 1 (40 mg cabozantinib + 1200 mg atezolizumab) and three RCC subjects at Dose Level 2 (60 mg cabozantinib + 1200 mg atezolizumab). At the time of the Cohort Review Committee meeting, all enrolled subjects of the Dose-Escalation Stage were active on study treatment. The longest follow-up of eight Cycles was for the first enrolled subject at Dose Level 1. There were no dose-limiting toxicities (DLTs) or serious adverse events (SAEs) at either dose level. The majority of observed AEs were of Grade 1 or Grade 2 severity. Grade 3 AEs regardless of causality included three events of hypertension, one event of hypophosphatemia, one event of diarrhea, and one event of PE (incidental asymptomatic finding). All reported AEs were consistent with the known safety profiles of either study treatment and were manageable with supportive care. At each cabozantinib dose level (40 mg and 60 mg), there was one dose reduction due to an AE. Adverse events which led to a dose reduction were one event of Grade 1 hand-foot syndrome (Dose Level 1 cabozantinib 40 mg) and one event of Grade 3 diarrhea (Dose Level 2 cabozantinib 60 mg). There was one dose delay of atezolizumab because of a Grade 1 irAE of hyperthyroidism (Dose Level 2). Encouraging preliminary clinical activity was observed at both dose levels with 1 CR, 2 PRs, and 3 stable diseases (SDs) among six subjects with available post-baseline tumor assessments. Because of a more favorable safety profile over a longer follow-up at Dose Level 1, the Cohort Review Committee determined that cabozantinib 40 mg qd orally in combination with 1200 mg atezolizumab q3w IV on the standard dosing schedule is the recommended dose and schedule for the Expansion Stage cohorts. Subjects enrolled at Dose Level 2 (60 mg cabozantinib + 1200 mg atezolizumab q3w IV) were allowed to continue on this dose if deemed tolerable per investigator judgment, and an additional 3 subjects were enrolled at this Dose Level to further explore tolerability and clinical activity.

On 03 April 2018, the Cohort Review Committee reviewed safety data of six subjects enrolled at Dose Level 2 (60 mg cabozantinib +1200 mg atezolizumab) with a longest follow-up to Cycle 6. At the time of the Cohort Review Committee meeting, all 12 enrolled RCC subjects of the Dose-Escalation Stage (6 subjects at each Dose Level) were active on study treatment. Among

the six subjects enrolled at Dose Level 2, there was no DLT or SAE reported. The majority of AEs at Dose Level 2 were of Grade 1 or 2 in severity. Grade 3 AEs included one event of hypertension, one event of diarrhea, and one event of hypophosphatemia. There was one irAE of Grade 1 hyperthyroidism, which required a dosing delay of atezolizumab, and one subject had a dose reduction from 60-mg to 40-mg cabozantinib.

On 21 July 2018 (preliminary safety data report) all 12 enrolled RCC subjects of the Dose-Escalation stage were still active on study treatment. The majority of AEs at both dose levels (cabozantinib 40 mg and 60 mg) were of Grade 1 and 2 in severity, and there were no Grade 4 or 5 events. Grade 3 AEs at Dose level 1 (cabozantinib 40 mg + atezolizumab 1200 mg) included hypertension (n=3), γ-glutamyltranspeptidase increased (irAE, n=1), hyperglycemia, hypophosphatemia, and PE (each n=1). Grade 3 AEs at Dose level 2 (cabozantinib 60 mg + atezolizumab 1200 mg) included diarrhea, hypertension (each n=2), ALT increased, AST increased, lipase increased (irAEs, each n=1), hypophosphatemia, and lymphocyte count decreased (each n=1). All AEs were manageable by dose modifications including dose reductions and dose delays as well as supportive care. Both assigned dose levels of cabozantinib 40 mg and 60 mg were well tolerated over extended dosing periods with no DLTs during the Dose-Escalation Stage, and confirmed responses were observed. However, there was a higher rate of dose reductions (cabozantinib) and dose delays (atezolizumab) in subjects enrolled at Dose Level 2, suggesting that the longer term tolerability of the combination was improved at Dose Level 1. The overall safety profile of each study treatment component remained consistent with previous reports.

As of 21 May 2019, 10 of the 12 subjects in the Dose-Escalation Stage continued study treatment, and two subjects discontinued study treatment more than 15 months after the first dose of study treatment.

A safety overview for the two dose level cohorts explored in the Dose-Escalation Stage as of 21 May 2019 is shown in the table below:

| Safety Event | Dose-Escalation Level 1: Cabozantinib 40 mg + Atezolizumab 1200 mg (N = 6) n (%) | Dose-Escalation Level 2: Cabozantinib 60 mg + Atezolizumab 1200 mg (N = 6) n (%) |
|---|---|---|
| Dose-limiting toxicity | 0 | 0 |
| Related AEs | 6 (100) | 6 (100) |
| Grade 3 or 4 AE | 5 (83) | 6 (100) |
| Immune-related AE | 1 (17) | 3 (50) |
| AE leading to cabozantinib dose reduction | 3 (50) | 6 (100) |
| AE leading to cabozantinib dose interruption | 3 (50) | 5 (83) |
| AE leading to cabozantinib discontinuation | 0 | 2 (33) |
| AE leading to atezolizumab discontinuation | 1 (17) | 1 (17) |
| Death | 0 | 0 |

AE, adverse event.

The Expansion Stage has been initiated (first subject enrolled on 26 March 2018) in multiple tumor cohorts with the recommended dose of the Dose-Escalation stage: cabozantinib 40 mg qd + atezolizumab 1200 mg q3w on the standard dosing schedule.

As of 21 May 2019, 268 subjects were enrolled across 18 Expansion Stage cohorts evaluating cabozantinib + atezolizumab in 12 different solid tumor types.

At the time of the data cutoff, safety data were available for 280 subjects across the Dose-Escalation Stage and 18 Expansion Stage cohorts. The most frequently reported AEs (≥ 20% incidence) of any grade in descending order of frequency regardless of causality were fatigue (30%), diarrhea (29%), nausea (24%), and decreased appetite (23%). Grade 4 AEs irrespective of causality were reported for 13 subjects, and Grade 5 AEs were reported for 20 subjects, including 3 treatment-related Grade 5 AEs. Three subjects died due to events assessed as related to either cabozantinib or atezolizumab: A 90-year-old male subject with CRPC developed severe protein-calorie malnutrition 18 days after initiating study treatment and died due to dehydration assessed as related to cabozantinib; a 58-year-old female subject with TNBC developed fatal pulmonary hemorrhage assessed as related to cabozantinib 23 days after initiating study treatment and following hospitalization for severe hyponatremia and

cardiopulmonary resuscitation for cardiac arrest; and a 45 year-old female subject with ovarian cancer died due to immune-mediated encephalitis assessed as related to atezolizumab 11 days after initiating study treatment.

An overview of subject incidence of AEs is provided in Table 1-1; the most frequent AEs regardless of causality (≥ 10%) are presented in Table 1-2; Immune-related AEs are summarized in Table 1-3.

**Table 1-1: Overall Safety Overview as of 21 May 2019 (Dose-Escalation Stage and Expansion Stage)**

| | **All Subjects (N = 280) n (%)** |
|---|---|
| Any AEs | 229 (82) |
| Immune-related AEs | 57 (20) |
| Related AEs | 199 (71) |
| Related Grade 3 or 4 AEs | 90 (32) |
| Related Grade 4 AEs | 6 (2.1) |
| Related Grade 5 AEs | 3 (1.1) |
| AEs leading to cabozantinib dose reduction | 65 (23) |
| AEs leading to cabozantinib discontinuation | 34 (12) |
| AEs leading to atezolizumab discontinuation | 24 (8.6) |
| Death | 44 (16) |

**Table 1-2: Summary of Frequent Adverse Events Regardless of Causality (≥ 10%) as of 21 May 2019 (Dose-Escalation Stage and Expansion Stage)**

| Preferred Term | Grand Total All Cohorts (N = 280) n (%) | | | |
|---|---|---|---|---|
| | Any Grade | Grade 3-4 | Grade 4 | Grade 5 |
| Number of subjects with at least one event | 229 (82) | 124 (44) | 13 (4.6) | 20 (7.1) |
| Fatigue | 83 (30) | 11 (3.9) | 0 | 0 |
| Diarrhoea | 82 (29) | 9 (3.2) | 0 | 0 |
| Nausea | 66 (24) | 2 (0.7) | 0 | 0 |
| Decreased appetite | 64 (23) | 3 (1.1) | 0 | 0 |
| Aspartate aminotransferase increased | 51 (18) | 7 (2.5) | 0 | 0 |
| Alanine aminotransferase increased | 48 (17) | 9 (3.2) | 0 | 0 |
| Constipation | 44 (16) | 1 (0.4) | 0 | 0 |
| Dysgeusia | 41 (15) | 1 (0.4) | 0 | 0 |
| Palmar-plantar erythrodysaesthesia syndrome | 40 (14) | 1 (0.4) | 0 | 0 |
| Asthenia | 38 (14) | 2 (0.7) | 0 | 0 |
| Hyponatraemia | 38 (14) | 17 (6.1) | 3 (1.1) | 0 |
| Hypertension | 37 (13) | 18 (6.4) | 0 | 0 |
| Headache | 35 (13) | 2 (0.7) | 0 | 0 |
| Vomiting | 35 (13) | 3 (1.1) | 0 | 0 |
| Stomatitis | 34 (12) | 1 (0.4) | 0 | 0 |
| Urinary tract infection | 31 (11) | 8 (2.9) | 0 | 0 |
| Weight decreased | 31 (11) | 1 (0.4) | 0 | 0 |

**Table 1-3: Summary of Immune-Related Adverse Events (≥ 1%) by Preferred Term and Severity as of 21 May 2019 (Dose-Escalation Stage and Expansion Stage)**

| Preferred Terms | Grand Total All Cohorts (N = 280) n (%) | | | |
|---|---|---|---|---|
| | Any Grade | Grade 3-4 | Grade 4 | Grade 5 |
| Number of subjects with at least one event | 57 (20) | 19 (6.8) | 2 (0.7) | 1 (0.4) |
| Diarrhoea | 7 (2.5) | 1 (0.4) | 0 | 0 |
| Hyperthyroidism | 7 (2.5) | 0 | 0 | 0 |
| Aspartate aminotransferase increased | 6 (2.1) | 3 (1.1) | 0 | 0 |
| Rash maculo-papular | 6 (2.1) | 2 (0.7) | 0 | 0 |
| Alanine aminotransferase increased | 5 (1.8) | 2 (0.7) | 0 | 0 |
| Arthralgia | 5 (1.8) | 2 (0.7) | 0 | 0 |
| Decreased appetite | 5 (1.8) | 1 (0.4) | 0 | 0 |
| Hypothyroidism | 5 (1.8) | 0 | 0 | 0 |
| Lipase increased | 5 (1.8) | 1 (0.4) | 0 | 0 |
| Pruritus | 5 (1.8) | 1 (0.4) | 0 | 0 |
| Amylase increased | 4 (1.4) | 0 | 0 | 0 |
| Fatigue | 4 (1.4) | 0 | 0 | 0 |
| Mucosal inflammation | 3 (1.1) | 0 | 0 | 0 |
| Vomiting | 3 (1.1) | 0 | 0 | 0 |

Upon evaluation of safety and efficacy data of approximately 30 initially enrolled subjects in each Combination-Therapy Expansion Cohort, the Study Oversight Committee (SOC) may recommend extending enrollment with up to 100 additional subjects to further evaluate the clinical activity and tolerability of the combination therapy in those selected tumor cohort(s) (see Section 3.5.2.1 for further details). Extended enrollment in a cohort may occur at Dose Level 1 (cabozantinib 40 mg + atezolizumab 1200 mg) or Dose Level 2 (cabozantinib 60 mg + atezolizumab 1200 mg) depending on the observed clinical activity and safety of the combination therapy with atezolizumab. Extended enrollment at Dose Level 1 may be recommended by the SOC for tumor cohort(s) with encouraging clinical activity (eg, meaningful ORR). Extended enrollment at Dose Level 2 may be recommended by the SOC for tumor cohort(s) which do not meet the criteria for Extended Enrollment Option 1 to explore whether the higher cabozantinib dose will lead to improved clinical activity and maintain an acceptable safety profile. After reviewing the safety and efficacy data of the first 30 enrolled subjects each in Expansion Cohort 1 (RCC), Expansion Cohort 6 (mCRPC), and Expansion Cohort 7 (NSCLC,

prior ICI-therapy) the SOC recommended extended enrollment for RCC Cohort 1 on 11 December 2018 with additional 30 subjects at Dose Level 2 and for mCRPC Cohort 6 and NSCLC Cohort 7 with 50 additional subjects at Dose Level 1 on 15 March 2019 and 09 July 2019, respectively.

Subjects with UC, NSCLC, and CRPC enrolled in the Exploratory SAC Cohorts of this study will be assigned to single-agent cabozantinib 60 mg, a dose anticipated to be clinically active. In addition to being the approved single-agent dose in RCC, the tolerability and clinical activity of single-agent cabozantinib 60 mg has also been established in multiple tumor indications such as advanced HCC, CRPC, UC, DTC, and NSCLC (Abou-Alfa et al 2018, Smith et al 2016, Apolo et al [J Clin Oncol] 2016, Cabanillas et al 2017, Drilon et al 2016). Enrollment of the SAC cohorts may be extended after review of safety and efficacy of the initially enrolled approximately 30 subjects if the SOC decides that additional subjects are required to determine the individual contribution of cabozantinib to the combination therapy.

Furthermore, an SAA cohort will initially enroll 10 subjects with advanced CRPC to receive single-agent atezolizumab with a standard dosing regimen (1200 mg IV q3w) to evaluate the individual contribution of atezolizumab to the combination therapy. Additional enrollment will be conditional upon responses among the first 10 enrolled subjects. If there are at least two confirmed responses (PR or CR) per RECIST 1.1 among the initial 10 subjects enrolled, up to 20 additional subjects may be enrolled for a total of 30 subjects in this cohort. No further enrollment extension will occur after 30 subjects have enrolled in the SAA cohort.

Subjects who radiographically progress (per Investigator per RECIST 1.1) on single-agent treatment in the SAC or SAA Cohorts may be able to receive combination treatment with cabozantinib and atezolizumab in the Second Agent Add-On Stage if they are deemed eligible. In this stage of the study, subjects will receive atezolizumab doses of 1200 mg IV q3w and cabozantinib doses at the lower of 40 mg by mouth (PO) qd or their most recently received dose level.

### 1.4 Overall Risk Benefit Assessment

The study will evaluate the safety, tolerability, and preliminary clinical activity of cabozantinib in combination with atezolizumab in tumor indications where at least one agent has either received regulatory approval or has demonstrated encouraging clinical activity in early stage trials (refer to Sections 1.1.1 and 1.2). In addition, a scientific rationale for a treatment combination of cabozantinib with an ICI has been established in both the preclinical and clinical settings (Kwilas et al 2014, Apolo et al 2014, Tolaney et al 2016). Further, encouraging

preliminary clinical activity and safety of cabozantinib in combination with a PD-1 targeting checkpoint inhibitor in ICI-naïve and ICI-pretreated subjects have been demonstrated in a Phase 1 study in subjects with GU cancer including metastatic UC and RCC (Nadal et al [Ann Oncol] 2017, Nadal et al 2018). In addition, in recent studies it has been demonstrated that an ICI in combination with cabozantinib or a TKI with a similar target profile as cabozantinib (inhibiting targets which regulate the immune system) was able to provide clinical benefit in cancer patients who progressed on prior ICI therapy (Nadal et al 2018, Leal et al 2017). The above suggests that combining ICI treatment with cabozantinib may result in a tumor microenvironment that is conducive to re-sensitization to ICI treatment after progression which could potentially address an important unmet medical need as the majority of cancer patients develop resistance and some patients are a priori refractory to ICI therapy.

Additionally, the safety and efficacy of cabozantinib administered as single-agent will be explored in UC and NSCLC subjects, who have been previously treated with ICIs, and CRPC subjects. As the safety and efficacy of cabozantinib administered as single-agent have also been established in other studies enrolling subjects with advanced UC, NSCLC, and CRPC (Apolo et al [J Clin Oncol] 2016, Drilon et al 2016; Smith et al 2016), a descriptive analysis of cabozantinib administered alone in the current study would be expected to provide valuable understanding of the individual contribution of cabozantinib to the clinical activity of the combination therapy.

Furthermore, the safety and efficacy of atezolizumab as single-agent will be evaluated in high-risk CRPC subjects. The analysis performed based on the data from this cohort will be expected to provide valuable understanding of the individual contribution of atezolizumab to the clinical activity of the combination therapy.

The safety profiles of both cabozantinib and atezolizumab are well described based on multiple clinical evaluations. During an initial standard “3 + 3” Dose-Escalation Stage, a tolerable dose and dosing schedule of cabozantinib that can be administered in combination with the standard dose of atezolizumab in this study population was determined by a Cohort Review Committee (Section 12.1). The recommended dose for the Combination-Therapy Cohorts in the Expansion Stage of the study will be evaluated across 20 tumor cohorts. Throughout the study, all enrolled subjects will have to undergo regular safety visits in order to ensure adequate management and reporting of AEs. An SOC will periodically review safety and efficacy data of the Expansion Stage and recommend further enrollment with up to an additional approximately 100 subjects each in the Combination-Therapy Expansion Cohorts and up to an additional approximately 50 subjects each in the SAC Cohorts after approximately 30 subjects have been enrolled

(Sections 9.1.2 and 12.2). The extended enrollment will be limited to up to 10 cohorts in the Expansion Stage excluding the SAA cohort. Extended enrollment beyond 30 subjects is not allowed in the SAA Cohort. The Sponsor's Executive Safety Committee (ESC; Section 12.3) will also periodically review safety data from all subjects enrolled in this study.

In order to minimize the safety risks to participating subjects, this protocol has eligibility criteria appropriate to the populations, and includes allowances for dose reductions (cabozantinib) and treatment delays (cabozantinib, atezolizumab). Periodic clinical assessments (physical examination, vital sign, and electrocardiographic assessments) and clinical laboratory tests will monitor for cabozantinib- and atezolizumab-related toxicities. Subjects will also be carefully monitored for AEs potentially related to inhibition of VEGFR by cabozantinib including gastrointestinal (GI) perforation, fistula formation, wound dehiscence, serious bleeding, proteinuria, hypertension, thromboembolic events, osteonecrosis, and reversible posterior leukoencephalopathy syndrome (RPLS) as well as immune-related side effects related to atezolizumab (pneumonitis, hepatitis, colitis, endocrinopathies, skin disorders, ocular events, neurological toxicity, pancreatitis, and infections).

Based on the clinical activity of cabozantinib and atezolizumab as single agents in multiple tumor types and the observed favorable tolerability and encouraging clinical activity of this combination in the Dose-Escalation Stage of this study, the potential benefit from cabozantinib administered alone or in combination with atezolizumab appears to outweigh the potential risks in subjects with advanced RCC, UC, CRPC, NSCLC, TNBC, OC, EC, HCC, GC/GEJC/LEC, CRC, head and neck squamous cell carcinoma (HNSCC), and DTC.

## 2 STUDY OBJECTIVES

Dose-Escalation Stage Combination Therapy Cohorts):

The primary objective is as follows:

- To determine the maximum tolerated dose (MTD) and/or recommended dose and schedule for the subsequent Expansion Stage of daily oral administration of cabozantinib in subjects with solid tumors when taken in combination with atezolizumab.

The secondary objective is as follows:

- To evaluate the plasma PK of daily oral administration of cabozantinib in subjects with solid tumors when given in combination with atezolizumab.
- To assess safety of the combination therapy through the evaluation of incidence and severity of nonserious AEs and serious adverse events (SAEs), including irAEs and AESIs.

The exploratory objective is as follows:

- Correlation of immune cell, tumor cell, and blood biomarker analyses with clinical outcome
- ORR as assessed by the Investigator per RECIST 1.1

Expansion Stage (Combination-Therapy Cohorts):

The primary objective and endpoint is as follows:

- To evaluate preliminary efficacy of the combination therapy by estimating the ORR as assessed by the Investigator per RECIST 1.1

The secondary objective is as follows:

- To assess safety for the combination therapy through the evaluation of incidence and severity of nonserious AEs and SAEs, including irAEs and AESIs.

The exploratory objectives and endpoints are as follows:

- ORR as assessed by the Investigator per irRECIST for immune response
- DOR as assessed by the Investigator per RECIST 1.1
- PFS as assessed by the Investigator per RECIST 1.1
- ORR, DOR, and PFS as assessed by a Blinded Independent Radiology Committee (BIRC) per RECIST 1.1 for selected cohorts
- Overall survival
- Correlation of immune cell, tumor cell, and blood biomarker analyses with clinical outcome
- Changes in tumor infiltration and/or histology or other molecular changes as determined from optional tumor biopsy
- To further evaluate the plasma PK of daily oral administration of cabozantinib in subjects with solid tumors when given in combination with atezolizumab
- Tumor marker changes from baseline in select tumor indications
- Evaluation of mismatch repair (MMR) and microsatellite instability (MSI) status in relevant tumor indications
- Changes in PSA from baseline for CRPC cohorts

<u>Exploratory Single-Agent Cabozantinib (SAC) Cohorts:</u>

- Descriptive efficacy, safety, PK, and biomarker analyses of SAC Cohorts in UC, CRPC, and NSCLC subjects
- Descriptive efficacy and safety analyses of combination therapy after progression on single-agent cabozantinib therapy

<u>Exploratory Single-Agent Atezolizumab (SAA) Cohort:</u>

- Descriptive efficacy, safety, PK, and biomarker analyses of SAA in CRPC subjects
- Descriptive efficacy and safety analyses of combination therapy after progression on single-agent atezolizumab therapy

# 3 STUDY DESIGN

## 3.1 Overview

This is a multicenter, open-label Phase 1b study to assess safety, tolerability, preliminary efficacy, and PK of cabozantinib taken alone or in combination with atezolizumab in subjects with advanced RCC, UC, CRPC, NSCLC, TNBC, OC, EC, HCC, GC/GEJC/LEC, CRC, H&N cancer, and DTC. This study consists of two stages for the combination therapy: the Dose-Escalation Stage and the Expansion Stage. In addition, the Expansion Stage will enroll SAC cohorts and an SAA cohort.

## 3.2 Study Sites

The Dose-Escalation Stage of this study will be conducted at up to 5 clinical sites in the US. Additional US, European, and Australian sites will be added (approximately 130 total sites) for the Combination-Therapy Cohorts, the SAC Cohorts, and the SAA Cohort in the Expansion Stage.

## 3.3 Blinding and Randomization

This is an open-label study with treatment arm assignment based upon currently enrolling dose level in the Dose-Escalation Stage and by tumor type and prior anticancer therapy in the Expansion Stage. There will be no blinding in this study.

In the Expansion Stage, Cohorts 5 and 19 (UC) have identical eligibility criteria, as do Cohorts 7 and 20 (NSCLC) and Cohorts 21-23 (high risk CRPC). Assignment of UC subjects to either Cohort 5 or 19, NSCLC subjects to either Cohort 7 or 20, and high-risk CRPC subjects to Cohort 21, 22, or 23 will be done by the Sponsor or designee. Subjects will be randomized, per an unstratified permuted block design, into the cohorts open to enrollment following the eligibility review process by the Sponsor. Randomized cohort assignment will be implemented as long as two or more cohorts with identical eligibility criteria are open to enrollment. Following confirmation of subject eligibility, Sponsor or CRO personnel will randomize subjects according to a centrally-maintained randomization list and enter the assigned cohort into the Interactive Response Technology (IRT).

Subjects are deemed to be enrolled in the study upon receipt of any study treatment. Subjects randomized who do not receive study treatment will not be considered enrolled into the study and will be classified as screen failures based upon the reason for not receiving treatment. Refer to Section 3.5.2 for cohort enrollment details.

### 3.4 Pretreatment Period

Potential subjects will be screened to determine if they meet eligibility criteria. Qualifying screening assessments must be performed within 28 days before first dose of study treatment unless otherwise stated (certain lab values must be obtained closer to first dose; see the schedules of assessment for details [Dose-Escalation Stage, Appendix A; Combination-Therapy Expansion Cohorts, SAC Cohorts, and SAA Cohort, Appendix B]).

### 3.5 Treatment Period

Subjects will receive study treatment as long as they continue to experience clinical benefit in the opinion of the investigator or until there is unacceptable toxicity, the need for subsequent systemic anticancer treatment, or until any other reasons for treatment discontinuation listed in the protocol (Section 3.8). Treatment may continue after radiographic progression as long as the Investigator believes that the subject is still receiving clinical benefit from study treatment and that the potential benefit of continuing study treatment outweighs potential risk. Clinical judgment should be used for allowing treatment beyond radiographic progression. Subjects with clinically significant symptomatic deterioration at the time of radiographic progression may not be suitable for further treatment. The possibility of a delayed anti-tumor immune response should be taken into consideration: mixed responses with decreasing and increasing tumor lesion sizes at the same imaging time point or the appearance of new lesions prior to achieving a radiological response have been reported with ICI. For subjects in combination treatment cohorts, discontinuation of one component of the combination study treatment while continuing to receive the other may be allowed with Sponsor notification. For cohorts where the initial dose is 40 mg cabozantinib, intra-subject dose escalation of cabozantinib from 40 mg to 60 mg is allowed after Sponsor approval for subjects who are tolerating the 40 mg cabozantinib dose level well and have been treated on this dose level for at least 4 weeks.

Subjects in the SAC and SAA cohorts who experience Investigator-assessed radiographic disease progression on single-agent therapy will be allowed to receive combination treatment with cabozantinib and atezolizumab provided they meet the eligibility criteria for combination treatment at that point (Second Agent Add-On Stage).

All enrolled subjects will be treated with best supportive care while on study treatment. This excludes systemic nonprotocol anticancer therapy, which requires study treatment to be discontinued. Permitted study drug modifications to manage AEs will comprise dose reductions (from 60 mg to 40 mg daily, from 40 mg to 20 mg daily, or from 20 mg daily to 20 mg every other day [qod]) or interruptions for cabozantinib and dose delays for atezolizumab.

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

### 3.5.1 Dose-Escalation Stage (Combination Therapy)

The primary objective of the Dose-Escalation Stage is to determine the MTD and/or the recommended Expansion Stage dose and schedule for cabozantinib when taken in combination with a standard dosing regimen of atezolizumab (1200 mg infusion, once every 3 weeks).

Three cabozantinib tablet daily dose levels will be considered for evaluation: 20 mg, 40 mg, and 60 mg. Atezolizumab will be administered as a 1200 mg infusion once every 3 weeks (Table 3-1).

The DLT Evaluation Period is defined as the 21 days following administration of the first dose of atezolizumab. Subjects will accrue in escalation cohorts of 3-6 subjects using a "3 plus 3" design, and dosing will begin at the 40 mg dose level of cabozantinib. Subjects with either advanced UC or RCC will be eligible for these cohorts, and cohorts may comprise mixtures of subjects with those tumor types. During this stage, the decision to open a new cohort will be made by the Cohort Review Committee when all subjects in the current cohort have completed the DLT Evaluation Period. Cohort enrollment decisions will depend largely upon DLT reporting for subjects through the DLT Evaluation Period, but all available safety and PK data will be considered in a decision to dose escalate or de-escalate the next cohort or expand the current cohort. Dose escalation/de-escalation decision rules based on DLTs are provided in Table 3-2, and DLT definitions are provided in Section 3.5.1.2. A subject who is withdrawn from the study for failing to receive the first dose of atezolizumab or at least 75% of the mandated doses of cabozantinib during the DLT Evaluation Period for reasons other than safety (eg, withdrawal of consent, non-compliance, disease progression, or AEs assessed as not related to study treatment) may be replaced.

**Table 3-1: Dosing Combinations for Potential Evaluation during the Dose-Escalation Stage**

| Relative Dose Level | Cabozantinib | Atezolizumab |
|---|---|---|
| 2 | 60 mg oral qd | 1200 mg IV q3w |
| 1 | 40 mg oral qd | 1200 mg IV q3w |
| -1 | 20 mg oral qd | 1200 mg IV q3w |

IV, intravenous; qd, once daily; q3w, once every three weeks

**Table 3-2: Dose-Escalation Stage Decision Rules**

| Number of Subjects per Cohort with DLTs in Current Cohort | Dose Escalation Decision Rule |
|---|---|
| 0 out of 3 | Enter three subjects at the next higher dose level. If the current dose level was not at the protocol-defined maximum cabozantinib dose (60 mg), the Cohort Review Committee may decide to enroll an additional three subjects at the current dose level in parallel. If the current cohort was treated at the protocol defined maximum cabozantinib dose (60 mg), enter an additional three subjects at that dose level. |
| 0 out of 6 | Hold further enrollment at the current dose level. |
| 1 out of 3 | Enter three more subjects at the current dose level. |
| 1 out of 6 | Enter three subjects at the next higher dose level unless evaluation of that dose level is already complete. If current cohort was treated at the protocol defined maximum cabozantinib dose level (60 mg), hold further enrollment in the Dose-Escalation Stage. |
| ≥ 2 out of 3 or 6 | Enter three additional subjects at the next lower dose level unless six subjects have already been treated at that level. If the current cohort was treated at the protocol-defined minimum cabozantinib dose level (20 mg), hold further enrollment in the Dose-Escalation Stage. |

DLT, dose-limiting toxicity.

An MTD of cabozantinib will be defined as the highest evaluated dose level at which not more than 1 out of 6 subjects experiences a DLT. As cabozantinib dose levels above 60 mg will not be evaluated, an MTD for cabozantinib may not be reached. The recommended dose for the Expansion Stage will be determined by the Cohort Review Committee based on DLTs observed during the DLT Evaluation Period and other relevant safety information.

Subjects in the Dose-Escalation Stage may continue to receive study treatment after completing the DLT Evaluation Period. The Cohort Review Committee will evaluate safety data collected during and after the DLT Evaluation Period to make informed decisions on cohort enrollment, dose escalation/de-escalation, and MTD or recommended dose and schedule determination.

#### 3.5.1.1 Dosing Schedules

Subjects in the Dose-Escalation Stage received study treatment on the Standard Dosing Schedule. Additional Dose-Escalation Stage cohorts following the Cabozantinib Run-In Dosing Schedule were not implemented by the Cohort Review Committee.

#### 3.5.1.1.1 Standard Dosing Schedule

Initial Dose-Escalation cohorts will receive the combination regimen on a "Standard Dosing Schedule" with the first infusion of atezolizumab given on the same day as the first dose of cabozantinib (on C1D1).

#### 3.5.1.1.2 Cabozantinib Run-In Dosing Schedule

If review of safety data for all enrolled subjects who received the Standard Dosing Schedule had not yielded a recommended dose for the Expansion Stage, the Cohort Review Committee had the option to enroll additional cohorts of subjects in the Dose-Escalation Stage treated on a "Cabozantinib Run-In Dosing Schedule." Subjects in these cohorts would have initiated treatment with cabozantinib on C1D1 and would have received their first infusion of atezolizumab 21 days later on Cycle 2 Day 1 (C2D1). The subjects would only have been evaluated for DLTs in the 21-day period after receiving the first infusion of atezolizumab (the DLT Evaluation Period). These cohorts would have been enrolled according to the "3+3" strategy described above, but the Cohort Review Committee could have included additional subjects at one or more dose levels in order to ensure enough subjects reached the DLT Evaluation Period while still receiving the assigned cohort dose (ie, experienced no dose reductions in the Cabozantinib Run-In Dosing Schedule). Administration of the first dose of atezolizumab was not to occur while cabozantinib treatment was interrupted; the start of Cycle 2 was to be delayed until after cabozantinib treatment had resumed, was well-tolerated, and the investigator determined that atezolizumab could be administered safely. If subjects discontinued cabozantinib treatment during Cycle 1 on the Cabozantinib Run-In Dosing Schedule, those subjects would not have been eligible to receive atezolizumab on study.

The purpose of this dosing schedule would have been to help the Cohort Review Committee assess whether subjects would have improved tolerability to the combination of cabozantinib and atezolizumab if first given the opportunity to optimize their tolerability to cabozantinib alone during a three week run-in period.

At the time of Protocol Amendment 2, following evaluation of the cohorts of subjects treated on the Standard Dosing Schedule in the Dose-Escalation Stage, the Cohort Review Committee did not deem it necessary to use the Cabozantinib Run-In Schedule.

#### 3.5.1.2 Dose-Limiting Toxicities

Dose-limiting toxicities will be determined by the Cohort Review Committee upon review of all available cohort data and are defined as any of the following occurring during the DLT Evaluation Period:

1. Any related AE that in the opinion of the Cohort Review Committee is of potential clinical significance such that further dose escalation of cabozantinib would expose subjects to unacceptable risk.

2. Any related ≥ Grade 3 AE which is unexpected in severity and/or duration compared with the known safety profiles of cabozantinib and atezolizumab when used as single agents, and that cannot be managed by dose modification (reduction or interruption), and adequate supportive care and requires permanent discontinuation of cabozantinib and/or atezolizumab.

3. Inability to take ≥ 75% of the planned cabozantinib dose during the DLT Evaluation Period because of a treatment-related AE

Examples of AEs which were not to be considered DLTs:

- Transient infusion-related AEs which can be controlled with medical management (ie, flu-like symptoms, fever)

- Tumor flare-related AEs (ie, localized pain, irritation at tumor sites)

- Any Grade 3 AE (regardless of relationship to study treatment) which the Cohort Review Committee determines is unlikely to compromise the subject's safety and resolves to ≤ Grade 1 or is controlled with adequate supportive care including short dose delays or dose reductions. These could include events that are expected to occur with single-agent therapy with cabozantinib or atezolizumab (ie, hypertension, skin toxicity, headache, nausea, fatigue, emesis, diarrhea).

- Single laboratory values that are out of normal range and unlikely to be related to study treatment and do not have any clinical correlate.

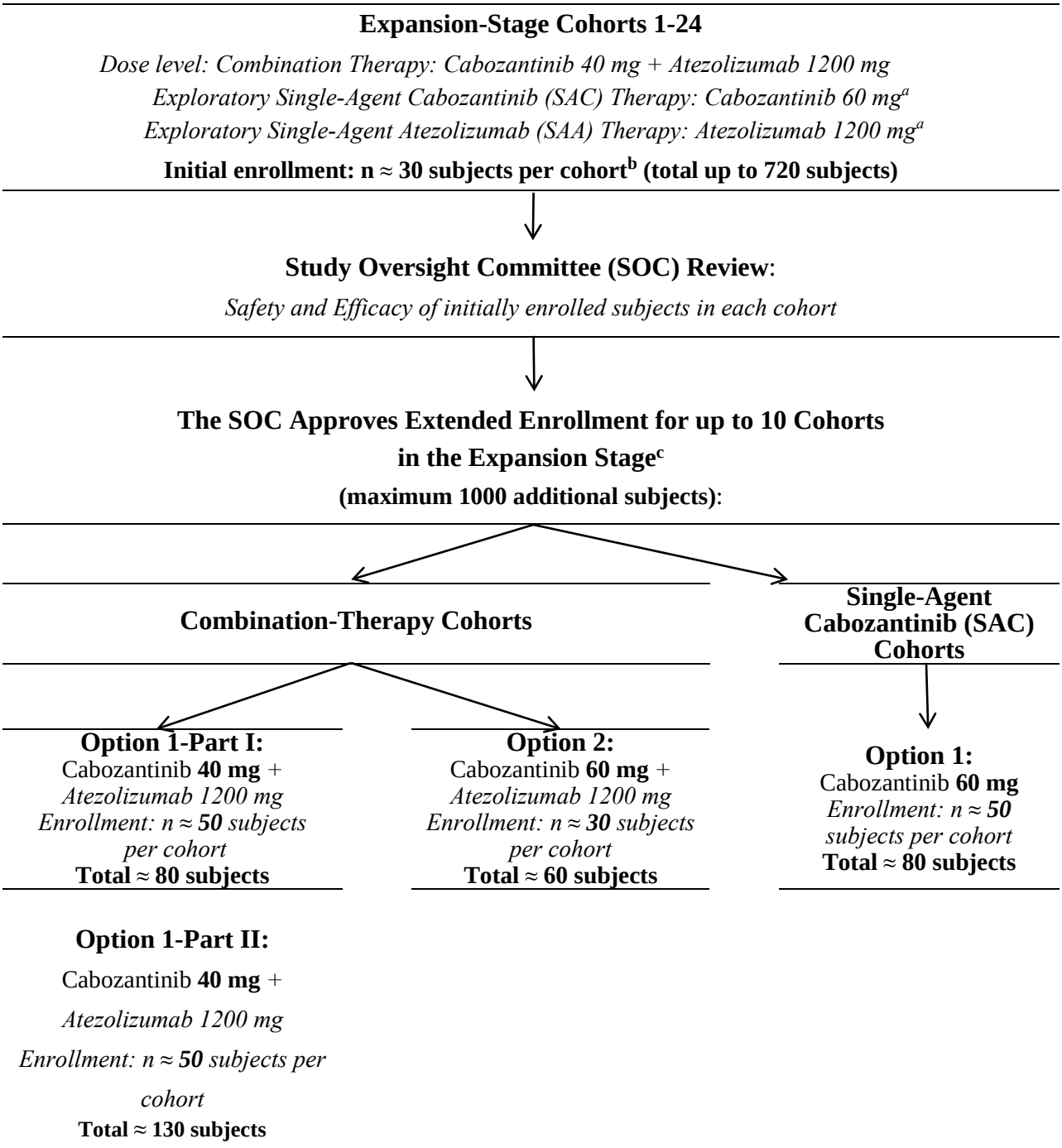
### 3.5.2 Expansion Stage (Combination-Therapy Cohorts, Exploratory Single-Agent Cabozantinib [SAC] Cohorts, and Exploratory Single-Agent Atezolizumab [SAA] Cohort)

The Expansion Stage will enroll 20 different tumor cohorts to evaluate the recommended dose of the combination therapy from the Dose-Escalation Stage. In addition, four single-agent cohorts will enroll subjects to receive either cabozantinib only (3 cohorts in UC, CRPC, and NSCLC) or atezolizumab only (one cohort in CRPC) to evaluate the individual contributions of the components of the combination therapy.

After initial enrollment of approximately 30 subjects, cohorts in the Expansion Stage except the SAA Cohort may extend enrollment based on the available clinical data per the SOC (Figure 3-1). Extended enrollment beyond 30 subjects is not allowed in the SAA Cohort. The extended enrollment will be limited to 10 cohorts in the Expansion Stage with a maximum extended enrollment of up to 1000 subjects.

Sections 3.5.2.1, 3.5.2.2, and 3.5.2.3 describe the study design for the Combination-Therapy Expansion Cohorts, SAC Cohorts, and SAA Cohort, respectively. An abbreviated description of Expansion Cohorts 1-18 and 23-24, SAC Cohorts 19-21, and SAA Cohort 22 is provided in Table 3-3. The SAC Cohorts and the SAA Cohort will open to enrollment at the discretion of the Sponsor. The Sponsor can decide to stop enrollment of any cohort at any time (eg, due to slow subject accrual). Subjects in SAC Cohorts and SAA Cohort may be eligible to receive combination therapy after Investigator-assessed radiographic disease progression per RECIST 1.1 on single-agent therapy as described in Section 3.5.2.4.

**Figure 3-1: Expansion Stage Enrollment Overview (Maximum 1720 Subjects)**




[a] Subjects who radiographically progress per RECIST 1.1 on single-agent treatment in the SAC or SAA Cohorts may be able to receive combination treatment with cabozantinib and atezolizumab in the Second Agent Add-On Stage if they are deemed eligible (see Section 3.5.2.4).

[b] In the SAA Cohort, an initial evaluation of clinical activity will be performed in the first 10 subjects prior to further enrollment in this cohort. Maximum enrollment of the SAA Cohort will be 30 subjects.

[c] Extended Enrollment is not allowed for SAA Cohort 22. Refer to Section 3.5.2.3 for subject enrollment in SAA Cohort 22.

**Table 3-3: Summary of All Combination-Therapy and Single-Agent Cohorts in the Expansion Stage**

| Cohort | Tumor Type (Histology) | Abbreviated Eligibility Description | Initial Cohort Size (n) |
|---|---|---|---|
| | | ***Combination-Therapy Cohorts*** | |
| 1 | RCC (clear cell) | No prior systemic anticancer therapy | 30 |
| 2 | UC (transitional cell) | Prior platinum-containing chemotherapy | 30 |
| 3 | UC (transitional cell) | Cisplatin-ineligible but no prior systemic anticancer therapy | 30 |
| 4 | UC (transitional cell) | Cisplatin-eligible but no prior systemic anticancer therapy | 30 |
| 5 | UC (transitional cell) | Prior immune checkpoint inhibitor therapy | 30 |
| 6 | CRPC (adeno) | Prior enzalutamide and/or abiraterone therapy | 30 |
| 7 | NSCLC (non-squamous) | Prior immune checkpoint inhibitor therapy | 30 |
| 8 | NSCLC (non-squamous) | No prior immune checkpoint inhibitor therapy | 30 |
| 9 | NSCLC (EGFR mutant, non-squamous) | Prior EGFR-targeting TKI therapy (prior immune checkpoint inhibitor therapy allowed if given in combination with chemotherapy) | 30 |
| 10 | RCC (non-clear cell) | Treatment naïve or prior systemic anticancer therapy | 30 |
| 11 | TNBC[a] (adeno) | Prior systemic anticancer therapy (prior immune checkpoint inhibitor therapy allowed) | 30 |
| 12 | OC[b] (epithelial) | Platinum-resistant or refractory | 30 |
| 13 | EC (serous or endometrioid) | Prior systemic anticancer therapy | 30 |
| 14 | HCC (adeno) | No prior systemic anticancer therapy | 30 |
| 15 | GC/GEJC/LEC (adeno) | Prior platinum- or fluoropyridine-containing therapy | 30 |
| 16 | CRC (adeno) | Prior fluoropyrimidine therapy with oxaliplatin or irinotecan | 30 |
| 17 | H&N (squamous) | Prior platinum-containing chemotherapy (prior immune checkpoint inhibitor therapy allowed) | 30 |
| 18 | DTC (follicular, papillary, and poorly differentiated) | No prior systemic anticancer therapy for radioiodine (RAI)-refractory disease | 30 |
| 23 | CRPC (adeno, high risk) | Prior enzalutamide or abiraterone therapy (no prior docetaxel initiated for mCRPC) | 30 |
| 24 | CRPC (adeno, high risk, prior chemo) | Prior enzalutamide and/or abiraterone therapy and prior taxane-based chemotherapy initiated for mCRPC | 30 |
| | | ***Exploratory SAC Cohort*** [c,d] | |
| 19 | UC (transitional cell) | Prior immune checkpoint inhibitor therapy | 30[c] |
| 20 | NSCLC (non-squamous) | Prior immune checkpoint inhibitor therapy | 30[c] |
| 21 | CRPC (adeno, high risk) | Prior enzalutamide or abiraterone therapy (no prior docetaxel initiated for mCRPC) | 30[c] |
| | | ***Exploratory SAA Cohort*** [d,e] | |
| 22 | CRPC (adeno, high risk) | Prior enzalutamide or abiraterone therapy (no prior docetaxel initiated for mCRPC) | 30[e] |
| | | **Total initial enrollment** | **720**[f] |

Adeno, adenocarcinoma; CRC, colorectal cancer; CRPC, castration-resistant prostate cancer; DTC, differentiated thyroid cancer; EC, endometrial cancer; EGFR, epidermal growth factor; GC/GEJC/LEC, gastric cancer, gastro-esophageal junction cancer, and lower esophageal cancer; H&N, head and neck cancer; HCC, hepatocellular cancer; HER-2, hormone epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer; OC, ovarian cancer; RCC, renal cell cancer; SAA, single-agent atezolizumab; SAC, single-agent cabozantinib; TKI, tyrosine kinase inhibitor; TNBC, triple-negative breast cancer; UC, urothelial cancer.

[a] Subjects' tumor samples must have tested negative for HER-2/neu, estrogen receptors, and progesterone receptors.

[b] The ovarian cancer cohort may also include subjects with primary peritoneal cancer and fallopian tube cancer.

[c] Exploratory SAC Cohorts may extend enrollment with approximately 50 additional subjects beyond the initially enrolled approximately 30 subjects per cohort per the SOC.

[d] Subjects in the SAC and SAA cohorts who radiographically progress per RECIST 1.1 on single-agent therapy will have the opportunity to receive combination treatment with cabozantinib and atezolizumab in the Second Agent Add-On Stage if they meet eligibility requirements (see Section 3.5.2.4)

[e] Exploratory SAA Cohort will initially enroll 10 subjects and may enroll up to 20 additional subjects for a maximum total of 30 subjects based upon the initial response among the first 10 enrolled subjects (see Section 3.5.2.3). Enrollment beyond 30 subjects in this cohort is not allowed.

[f] Approximately 30 subjects may be initially enrolled into each of the Combination-Therapy Expansion Cohorts and SAC Cohorts. Up to 10 cohorts in the Expansion Stage except the SAA Cohort (see footnote **e** above) may enroll up to an additional approximately 100 subjects each in the Combination-Therapy Cohorts and/or up to an additional approximately 50 subjects each in the SAC Cohorts.

#### 3.5.2.1 Combination-Therapy Expansion Cohorts

On 22 February 2018, the Cohort Review Committee identified the recommended dose and schedule of cabozantinib in combination with atezolizumab in the Dose-Escalation Stage and opened accrual in the Expansion Stage in March 2018. In this stage, 20 Combination-Therapy Expansion Cohorts in subjects with advanced RCC, UC, CRPC, NSCLC, TNBC, OC, EC, HCC, GC/GEJC/LEC, CRC, HNSCC, and DTC will be enrolled to obtain additional efficacy, safety, PK, and pharmacodynamic data at the recommended dose and schedule (the Standard Dosing Schedule) of cabozantinib in combination with atezolizumab. An abbreviated description of Expansion Cohorts 1-18 and 23-24 is provided in Table 3-3.

All Combination-Therapy Expansion Cohorts will initially enroll approximately 30 subjects (600 subjects in total).

Because of the high unmet medical need of patients with advanced, incurable cancer, the SOC may decide after periodic review of safety and efficacy data of the initially enrolled subjects in each Combination-Therapy Expansion Cohort to allow for additional enrollment to further assess the clinical activity and safety of the combination therapy.

Extended enrollment of a Combination-Therapy Expansion Cohort will be based on only one of the following two Extended Enrollment Options (see Figure 3-1):

- Extended Enrollment Option 1:
  - Part I: Combination-Therapy Expansion Cohorts may enroll approximately 50 additional subjects to receive the same dosing regimen as the initially enrolled approximately 30 subjects (cabozantinib 40 mg + atezolizumab 1200 mg) upon approval by the SOC. Decisions by the SOC regarding additional enrollment will be based on the clinical significance of the achieved ORR in the Expansion Cohorts and will include an evaluation of the lower bound of confidence intervals for ORR in the originally enrolled subjects. A minimum observed ORR of around 20% or more will be used as a target (though not a requirement) for the SOC to consider Part I of Extended Enrollment Option 1 (Section 9.1.2.1). The magnitude of ORR deemed clinically meaningful by the SOC may vary by cohort. The committee may also consider other factors of clinical benefit (eg, time to response, duration of response, safety/tolerability) in the decision to extend enrollment.

- Part II: Combination-Therapy Expansion Cohorts may further enroll approximately 50 additional subjects for a maximum total of approximately 130 subjects in an expansion cohort. These subjects will receive the same dosing regimen as the previously enrolled subjects (cabozantinib 40 mg + atezolizumab 1200 mg) upon approval by the SOC. Decisions by the SOC regarding further extended enrollment in Part II of Extended Enrollment Option 1 will be based on the clinical significance of the achieved ORR in the Expansion Cohorts and will include an evaluation of the lower bound of confidence intervals for ORR in the previously enrolled subjects. A minimum observed ORR of around 35% or more will be used as a target (though not a requirement) for the SOC to consider Part II of the Extended Enrollment Option 1 (Section 9.1.2.1). Part II extension will only apply to tumor indications with a high-unmet medical need and very encouraging efficacy and safety data observed in Part I.

- Extended Enrollment Option 2: For Combination-Therapy Expansion Cohorts in which the initially enrolled approximately 30 subjects do not meet the criteria for Extended Enrollment Option 1, the SOC may decide to allow each selected Expansion Cohort to enroll approximately 30 additional subjects to receive the highest dose level of cabozantinib explored in the Dose-Escalation Stage (60 mg) in combination with atezolizumab 1200 mg to explore whether the higher cabozantinib dose will lead to improved clinical activity and maintain an acceptable safety profile.

Details about the composition, role, schedule, and guidance for committee decisions are provided in a separate SOC Charter.

All subjects enrolled in the Expansion Cohorts will be following the same frequency of assessments as described in Appendix B with the exception of the DTC Cohort (Expansion Cohort 18) which follows a different tumor imaging schedule (see Appendix B). For more details regarding the eligibility of subjects in the Expansion Cohorts refer to inclusion and exclusion criteria (Sections 4.2 and 4.3). Rationales for enrollment in each Expansion Cohort are provided in Section 1.3.1.

#### 3.5.2.2 Exploratory Single-Agent Cabozantinib (SAC) Cohorts

Three SAC Cohorts (19, 20, and 21) will each enroll approximately 30 subjects with advanced UC, NSCLC, or CRPC, respectively (see Table 3-3 for a summary of SAC Cohorts). Subjects in the SAC Cohorts will receive single-agent cabozantinib 60 mg qd. The SOC may decide whether more subjects are needed to identify the contribution of cabozantinib to the combination treatment based on the results from the matching combination therapy cohorts. Each of these

cohorts will be allowed to enroll approximately 50 additional subjects at the same dosing regimen of cabozantinib as the initially enrolled subjects. The SAC Cohorts will open for enrollment at the discretion of the Sponsor. The Sponsor can decide to stop enrollment in the SAC cohorts at any time (eg, due to slow subject accrual).

All subjects enrolled in the SAC Cohorts will be following the same frequency of assessments as presented in Appendix B. For more details regarding the eligibility of subjects in the SAC Cohorts refer to inclusion and exclusion criteria (Sections 4.2 and 4.3). Rationales for enrollment in each SAC Cohort are provided in Section 1.3.1.

Subjects enrolled in the SAC cohorts who exhibit Investigator-assessed radiographic progression per RECIST 1.1 following treatment with single-agent cabozantinib may be eligible to receive the combination therapy in the Second Agent Add-On Stage. Please see Section 3.5.2.4 for details.

#### 3.5.2.3 Exploratory Single-Agent Atezolizumab (SAA) Cohort

SAA Cohort 22 will initially enroll 10 subjects with advanced CRPC (see Table 3-3) since there are limited data available on the clinical activity of atezolizumab in previously treated mCRPC (Kim et al 2018). Additional enrollment will be conditional upon responses observed among the first 10 enrolled subjects. If there are at least two confirmed responses (PR or CR) per RECIST 1.1 among the initial 10 subjects enrolled, up to 20 additional subjects may be enrolled for a maximum total of 30 subjects in this cohort. Subjects in this cohort will receive the standard dosing regimen of atezolizumab (1200 mg IV, q3w). Extended enrollment beyond 30 subjects is not allowed in this cohort. The SAA Cohort will open for enrollment at the discretion of the Sponsor. The Sponsor can decide to stop enrollment in this cohort at any time (eg, due to slow subject accrual).

Subjects in the SAA Cohort will be following the schedule of assessments presented in Appendix B. For more details regarding the eligibility of subjects in the SAA Cohort refer to inclusion and exclusion criteria (Sections 4.2 and 4.3). Rationales for enrollment in the SAA Cohort are provided in Section 1.3.1.

Subjects enrolled in the SAA cohort who exhibit Investigator-assessed radiographic progression per RECIST 1.1 following treatment with single-agent atezolizumab may be eligible to receive the combination therapy in the Second Agent Add-On Stage. Please see Section 3.5.2.4 for details.

#### 3.5.2.4 Second Agent Add-On Stage (For Subjects Enrolled in Single-Agent Cohorts)

Subjects enrolled into SAA or SAC cohorts 19, 20, 21, or 22 may have the option to be treated with combination therapy (cabozantinib and atezolizumab) after documented Investigator-assessed radiographic progression per RECIST 1.1 following treatment with single-agent therapy. To be eligible to receive combination treatment, subjects must tolerate single-agent therapy per Investigator assessment, meet the eligibility criteria as outlined in Appendix C, and receive Sponsor approval to enter the Second Agent Add-On Stage.

Subjects will continue single-agent therapy through the time radiographic progression has been documented and until Sponsor approval to begin combination therapy is received through IRT.

- Subjects moving to combination therapy from the SAC cohorts who were still receiving 60 mg cabozantinib qd doses will reduce to 40 mg cabozantinib qd doses in the Second Agent Add-On Stage; subjects who were receiving cabozantinib doses of 40 mg qd, 20 mg qd, or 20 mg qod will continue to receive cabozantinib at their current dose level. All these subjects will initiate atezolizumab treatment at 1200 mg IV, q3w.

- Subjects moving to combination therapy from the SAA cohort will continue to receive atezolizumab according to the standard regimen (1200 mg IV, q3w) and will initiate cabozantinib treatment at 40 mg orally, qd.

The dose modification guidelines for combination treatment in the Second Agent Add-On Stage are presented in Section 6.5.1.

Before subjects initiate combination treatment in the Second Agent Add-On Stage, a new baseline tumor status will be required as described in Section 5.6.9.1. Subjects will be evaluated according to the schedule of assessments provided in Appendix C. Subjects on the SAC and SAA cohorts who are not eligible for the Second Agent Add-On Stage or elect not to enter that stage of the study are to continue to follow the schedule of assessments provided in Appendix B.

### 3.6 Post-Treatment Period and Survival Follow-up

The final safety assessment will occur at the Post-Treatment Follow-Up Visit 30 (+14) days after the date of the decision to discontinue treatment. If a subject is experiencing an ongoing treatment-related AE that led to study treatment discontinuation, SAE, or AESI at the time of that visit, the subject will continue to be followed until the AE has resolved, the AE has improved to Grade 2 or lower, or the Investigator determines that the event has become stable or irreversible. During the Post-Treatment Period, each subject will continue to be followed for survival. The Investigator (or designee) will make contact (eg, in person or by telephone) with

the subject at least as frequently as every 12 weeks (± 14 days) after the Post-Treatment Follow-Up Visit, until the subject expires or the Sponsor decides to discontinue collection of these data for the study.

### 3.7 Maintenance Phase

The purpose of the Maintenance Phase is to continue to provide long-term access to study drug(s) to subjects who are deriving clinical benefit even after evaluation of the study objectives has been completed. When sufficient data have been collected to adequately evaluate all study endpoints, and upon site notification by the Sponsor, subjects remaining on study treatment or who have not completed the Post-Treatment Follow-Up Visit will enter the study Maintenance Phase. In the Maintenance Phase subjects who remain on treatment will continue to receive study treatment until a protocol-defined criterion for discontinuation has been met. With Sponsor notification, subjects in combination treatment cohorts may be allowed to discontinue one component of study treatment but continue to receive the other. After implementation of the Maintenance Phase, the study will be considered complete at sites and in countries that no longer have active subjects.

In the Maintenance Phase, subjects are to undergo periodic safety assessments (including local laboratory tests) and tumor assessments; the nature and frequency of these assessments are to be performed per standard of care if allowed by local regulations. It is the Investigator's responsibility to ensure that subject visits occur frequently enough and adequate assessments are performed to ensure subject safety. In order to continue to collect important safety information on subjects still enrolled in the study, reporting of SAEs; AEs (including irAEs), whether serious or not, leading to dose modifications or treatment discontinuation; AESIs; and other reportable events (pregnancy and medication errors with sequelae) is to continue per protocol requirements specific to the Maintenance Phase (Section 5.4).

Assessments in the Post-Treatment Period (including the Post-Treatment Follow-Up Visit) are not required for subjects who discontinue study treatment in the Maintenance Phase (such subjects are to be followed per standard of care). Further details are available in Appendix D.

### 3.8 Treatment Discontinuation and Withdrawals

Subjects may discontinue study treatment and assessments or withdraw their consent to participate in the study at any time without prejudice. When subjects withdraw consent, all study treatments will be stopped. The investigator may withdraw a subject from study treatment or from the study 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. The investigator will also withdraw a subject from

study treatment or from the study upon the Sponsor's request or if the Sponsor chooses to terminate the study.

Any of the following conditions require withdrawal of the subject from study treatment:

- Subject no longer experiences clinical benefit as determined by the investigator (eg, disease progression and/or clinical deterioration attributable to disease progression of which both are unlikely to reverse with continued study treatment and/or supportive care). However, subjects who radiographically progress per RECIST 1.1 on single-agent treatment in the SAC or SAA cohorts may be allowed to receive combination treatment in the Second Agent Add-On Stage if they meet the eligibility requirements provided in Appendix C.
- Unacceptable side effects the investigator feels may be due to study treatment. However, discontinuation of one component of the combination study treatment while continuing to receive the other may be allowed for subjects in combination treatment cohorts with Sponsor notification in an effort to manage such side effects in subjects experiencing clinical benefit.
- The investigator feels it is not in the best interest of the subject to continue on study.
- Subject participation in another clinical study using an investigational agent, investigational medical device, or other intervention.
- Necessity for treatment with nonprotocol systemic anticancer therapy.
- Necessity for interrupting all study treatment for greater than 12 weeks for study-treatment related AEs unless approved by the Sponsor. (Note: temporary interruptions of study treatment for greater than 12 weeks due to the effects of COVID-19 and unrelated to AEs are described in Appendix M)
- Refusal of sexually active fertile subjects (excluding subjects who have been sterilized) to use highly effective methods of contraception (Appendix K).
- Female subjects who become pregnant.
- Subject request to discontinue study treatment (with or without concurrent withdrawal of informed consent).
- Significant noncompliance with the protocol schedule in the opinion of the investigator or the Sponsor.

The Sponsor should be notified of all subject study treatment discontinuations and study withdrawals as soon as possible. The reason for discontinuation or withdrawal will be documented.

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 subsequent anticancer treatment unless consent to participate in the study is also withdrawn.

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 should be sent to the subject (or the subject's legal guardian) requesting contact with the clinic.

If a subject is discontinued from study treatment because of an AE (including irAE) considered to be related to study treatment and the event is ongoing at the time of the Post-Treatment Follow-Up Visit 30 (+14) days after the date of the decision to discontinue treatment (see Section 5.3 for further details), the event must be followed until resolution or determination by the investigator that the event has become stable or irreversible.

If a subject withdraws consent to participate in the study, no further study procedures or assessments will be performed and no further study data will be collected for this subject other than the determination of survival status for subjects enrolled in the Expansion Stage. This information may be obtained from public records such as government vital statistics or obituaries, as permitted by local law.

### 3.9 Subject Replacements

Only subjects who sign the informed consent and receive any study treatment will be considered enrolled.

During the Dose-Escalation Stage, if an enrolled subject fails to receive the first dose of atezolizumab or at least 75% of the mandated doses of cabozantinib during the DLT Evaluation Period for reasons other than safety (eg, withdrawal of consent, non-compliance, disease progression, or AEs assessed as not related to study treatment), he or she will be replaced (ie, an additional subject will be added to the cohort). Subjects who receive atezolizumab but fail to complete DLT Evaluation Period because of an AE related to study treatment will not be replaced. Subjects who are replaced with new subjects will not be considered in making dose escalation decisions, but if possible will be followed for safety and other assessments.

Subjects enrolled in the Expansion Stage will not be replaced.

# 4 STUDY POPULATION

## 4.1 Target Population

This study will enroll subjects with advanced solid tumors. The precise populations with these tumor types will vary between/within the Dose-Escalation Stage and cohorts in the Expansion Stage (Combination-Therapy Expansion Cohorts, SAC Cohorts, and SAA Cohort). 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 of the inclusion criteria and none of the exclusion criteria. The Sponsor will not grant waivers to study eligibility criteria.

*Of note, in the eligibility criteria described below, maintenance anticancer therapy after the initial anticancer therapy does not count towards the limit of prior systemic therapies, provided there is no tumor progression between the initial anticancer therapy and the start of maintenance anticancer therapy. In addition, radiosensitization chemotherapy and retreatment with the same anticancer agent do not count towards the limit of prior systemic therapies.*

*In the Expansion Stage, Cohorts 5 and 19 (UC) have identical eligibility criteria, as do Cohorts 7 and 20 (NSCLC) and Cohorts 21-23 (high risk CRPC).*

## 4.2 Inclusion Criteria

A subject must meet all of the following criteria to be eligible for the study:

1. Cytologically or histologically and radiologically confirmed solid tumor that is inoperable locally advanced, metastatic, or recurrent:

   Dose-Escalation Stage:

   a. Subjects with UC (including renal pelvis, ureter, urinary bladder, urethra) after prior platinum-based therapy, or

   b. Subjects with RCC (clear cell, non-clear cell histology) with or without prior systemic anticancer therapy

   Expansion Stage:

   c. Expansion Cohort 1**:** Subjects with RCC with clear cell histology (including those with mixed sarcomatoid component) and without prior systemic anticancer therapy for inoperable locally advanced or metastatic disease.

   d. Expansion Cohort 2**:** Subjects with UC with transitional cell histology (including renal pelvis, ureter, urinary bladder, urethra) who have radiographically progressed on or after platinum-containing chemotherapy including subjects who received prior neoadjuvant or adjuvant platinum-containing therapy with disease recurrence < 12 months from the end of last therapy.

e. Expansion Cohort 3: Subjects with UC with transitional cell histology (including renal pelvis, ureter, urinary bladder, urethra) who are ineligible for cisplatin-based chemotherapy and have not received prior systemic anticancer therapy for inoperable locally advanced or metastatic disease.

   - *Ineligible for cisplatin-based chemotherapy is defined by meeting one of the following criteria:*

     *Impaired renal function (glomerular filtration rate [GFR] < 60 mL/min/1.73 $m^2$), hearing loss of ≥ 25 dB at two contiguous frequencies, or ≥ Grade 2 peripheral neuropathy per Common Terminology Criteria for Adverse Events (CTCAE) v4.*

   - *Prior neoadjuvant or adjuvant platinum-based chemotherapy is allowed if disease recurrence took place > 12 months from end of last therapy.*

f. Expansion Cohort 4: Subjects with UC with transitional cell histology (including renal pelvis, ureter, urinary bladder, urethra) eligible for cisplatin-based chemotherapy and have not received prior systemic anticancer therapy for inoperable locally advanced or metastatic disease.

   - *Prior neoadjuvant or adjuvant platinum-based chemotherapy is allowed if disease recurrence took place > 12 months from end of last therapy.*

g. Expansion Cohort 5: Subjects with UC with transitional cell histology (including renal pelvis, ureter, urinary bladder, urethra) who have radiographically progressed on or after one prior immune checkpoint inhibitor (anti-PD-1 or anti-PD-L1) for the treatment of inoperable locally advanced or metastatic disease.

   - *Allowed are up to 2 lines of prior systemic anticancer therapy to treat inoperable locally advanced or metastatic UC including prior treatment with an anti-CTLA-4 agent.*

   - *Excluded are subjects who had a prior combination therapy of an immune checkpoint inhibitor (anti-PD-1 or anti-PD-L1) with a VEGFR-targeting TKI.*

h. Expansion Cohort 6: Subjects with metastatic CRPC (adenocarcinoma of the prostate without small cell component; neuroendocrine differentiation and other histologic components are permitted if adenocarcinoma is the primary histology) who have radiographically progressed in soft tissue on or after enzalutamide and/or abiraterone acetate for metastatic disease.

   (Note: PSA progression or bone progression alone are not allowed to determine eligibility).

   - *Prior chemotherapy is not allowed with the exception of docetaxel given in combination with androgen deprivation therapy (ADT) for progressive castration-sensitive disease prior to treatment with enzalutamide and/or abiraterone acetate.*

   - *Subject must have castrate-level testosterone (< 50 ng/dL [< 1.73 nM]) following bilateral orchiectomy or by ongoing androgen deprivation therapy with a gonadotropin-releasing hormone (GnRH) analog that was initiated ≥ 4 weeks prior to first dose of study treatment and must be continued throughout the study.*

i. Expansion Cohort 7: Subjects with Stage IV non-squamous NSCLC who have radiographically progressed on or after treatment with one prior immune checkpoint inhibitor (anti-PD-1 or anti-PD-L1) for metastatic disease.

   - *Allowed are up to 2 lines of prior systemic anticancer therapy to treat metastatic NSCLC including prior treatment with an anti-CTLA-4 agent.*
   - *Excluded are subjects who had a prior VEGFR-targeting TKI*
   - *Excluded are subjects who have been diagnosed with an EGFR sensitizing mutation, ALK rearrangement, ROS1 rearrangement, or BRAF V600E mutation.*

j. Expansion Cohort 8: Subjects with Stage IV non-squamous NSCLC with positive PD-L1 expression (TC ≥ 1% [TC = tumor cell]) and without prior systemic anticancer therapy for metastatic disease.

   - *Acceptable reports for prior PD-L1 expression testing by immunohistochemical (IHC) assessment include the following:*
     - *US sites: FDA-approved Dako PD-L1 IHC 22C3 pharmDx assay*
     - *Ex-US sites: health authority-approved or CE-marked Dako PD-L1 IHC 22C3 pharmDx assay*
   - *A prior local laboratory PD-L1 report using a validated assay may be accepted if slides can be provided to the central laboratory to assess PD-L1 expression using the FDA-approved Dako PD-L1 IHC 22C3 pharmDx assay.*

   *Excluded are subjects who have been diagnosed with an EGFR sensitizing mutation, ALK translocation, ROS1 rearrangement, or BRAF V600E mutation.*

k. Expansion Cohort 9: Subjects with Stage IV nonsquamous NSCLC with documentation of a sensitizing EGFR mutation who have radiographically progressed during or following prior treatment with at least one EGFR-targeting TKI (eg, osimertinib, gefitinib, erlotinib, afatinib) for metastatic disease.

   - *There is no limit on the number of prior lines of systemic anticancer therapy including chemotherapy for inoperable locally advanced, recurrent, or metastatic disease.*
   - *Prior treatment with ICIs (anti-PD-1 or anti-PD-L1) is allowed if given in combination with chemotherapy.*

l. Expansion Cohort 10: Subjects with RCC with non-clear cell histology (including those with sarcomatoid component)

   - *Allowed is prior therapy with up to one VEGFR-targeting TKI (eg, sunitinib, pazopanib) for inoperable locally advanced, recurrent, or metastatic disease.*
   - *TKIs targeting MET or prior therapy with immune checkpoint inhibitors is not allowed.*

m. Expansion Cohort 11: Subjects with breast cancer that has tested negative for hormone epidermal growth factor receptor 2 (HER-2), estrogen receptors, and progesterone receptors (ie, triple-negative breast cancer [TNBC]) who have radiographically

progressed during or following treatment with at least one prior systemic anticancer therapy for inoperable locally advanced, recurrent, or metastatic disease.

- *Allowed are up to 2 lines of prior systemic anticancer therapy for inoperable locally advanced, recurrent, or metastatic disease.*
- *Prior treatment with ICIs (anti-PD-1 or anti-PD-L1) is allowed.*
- *HER-2 negativity is defined as either of the following by local laboratory assessments:*
  - *In situ hybridization (ISH) non-amplified (ratio of HER-2 to CEP17 < 2.0 or single probe average HER-2 gene copy number < 4 signals/cell), or*
  - *IHC 0 or IHC 1+ (if more than one test result is available and not all results meet the inclusion criterion definition, all results should be discussed with the Sponsor to establish eligibility of the patient).*
- *Estrogen receptor (ER) and progesterone receptor (PR) negativity are defined as < 1% of cells expressing hormonal receptors via IHC analysis.*

n. Expansion Cohort 12: Subjects with epithelial ovarian cancer, including primary peritoneal cancer (PPC) and fallopian tube cancer (FTC) who have platinum-resistant or refractory disease.

- *Platinum- resistant disease is defined as disease progression within 6 months of receiving the last platinum dose. Platinum-refractory disease is defined as disease progression during platinum-based chemotherapy or within 4 weeks of the last platinum dose. Subjects who discontinue platinum-based therapy due to an adverse event cannot be defined as platinum-resistant or refractory and are therefore not eligible.*
- *Allowed are up to 2 lines of prior systemic anticancer therapy for inoperable locally advanced, recurrent, or metastatic disease. Hormonal therapies and intraperitoneal anticancer therapies are not counted towards prior treatment restrictions.*
- *Ovarian borderline epithelial tumors (low malignant potential) are excluded.*

o. Expansion Cohort 13: Subjects with endometrial cancer of serous or endometrioid histology who have radiographically progressed during or following treatment with at least one prior systemic anticancer therapy for inoperable locally advanced, recurrent, or metastatic disease.

- *Allowed are up to 2 lines of prior systemic anticancer therapy for inoperable locally advanced, recurrent, or metastatic disease.*
- *Hormonal therapies are not counted towards prior treatment restrictions.*

p. Expansion Cohort 14: Subjects with advanced HCC who have a Child-Pugh score of A (Appendix L) and have not received prior systemic anticancer therapy for inoperable locally advanced, recurrent, or metastatic disease.

- *Subjects with active hepatitis B virus (HBV) infection (defined by HBsAg positive) must be on standard of care antiviral therapy and have HBV DNA < 500 IU/mL.*

- *Prior local-regional treatment (eg, radiofrequency ablation, transcatheter arterial chemoembolization [TACE]) is allowed.*

q. Expansion Cohort 15: Subjects with gastric cancer, gastroesophageal junction adenocarcinoma, or lower one-third esophageal adenocarcinoma who have radiographically progressed during or following platinum-containing or fluoropyrimidine-containing chemotherapy for inoperable locally advanced, recurrent, or metastatic disease.

   - *Allowed are up to 2 lines of prior systemic anticancer therapy for inoperable locally advanced, recurrent, or metastatic disease.*
   - *Prior HER-2/neu directed therapy is allowed.*

r. Expansion Cohort 16: Subjects with colorectal adenocarcinoma who have radiographically progressed during or following systemic chemotherapy that contained fluoropyrimidine in combination with oxaliplatin or irinotecan for metastatic disease.

   - *Allowed are up to 2 lines of prior systemic anticancer therapy for inoperable locally advanced, recurrent, or metastatic disease.*
   - *Prior EGFR-targeted therapy is allowed.*
   - *Subjects with known microsatellite instability-high (MSI-H) and/or mismatch repair (MMR) deficient disease are excluded.*

s. Expansion Cohort 17: Subjects with head and neck cancer of squamous cell histology who have radiographically progressed during or following prior platinum-containing chemotherapy for inoperable locally advanced, recurrent, or metastatic disease.

   - *Allowed primary tumor locations: oropharynx, oral cavity, hypopharynx, or larynx. Excluded are subjects with primary tumor site of the nasopharynx*
   - *Allowed are up to 2 lines of prior systemic anticancer therapy for inoperable locally advanced, recurrent, or metastatic disease.*
   - *Prior treatment with ICIs (anti-PD-1 or anti-PD-L1) is allowed.*
   - *Prior EGFR-targeted therapy and radiotherapy concurrent or sequential with chemotherapy is allowed.*
   - *Results from testing of HPV status for oropharyngeal cancers should be provided but are not required for eligibility.*

t. Expansion Cohort 18: Subjects with DTC (follicular, papillary, and poorly differentiated histologies) who are radioactive iodine (RAI) refractory or deemed ineligible for treatment with RAI.

   - *Subjects who have received prior systemic anticancer therapy for RAI-refractory disease are not allowed.*
   - *Subjects must be receiving thyroxine suppression therapy, and TSH must be below the lower cutoff of the reference range or less than 0.50 mIU/L (< 0.50 µIU/mL), whichever is lower, within 28 days before enrollment. (Note: If hormone replacement therapy is tolerated, a TSH level of ≤ 0.1 mIU/L (≤ 0.1 µIU/mL) should be targeted.)*

u. Exploratory Single-Agent Cabozantinib (SAC) Cohort 19: Subjects with UC with transitional cell histology (including renal pelvis, ureter, urinary bladder, urethra) who have radiographically progressed on or after one prior immune checkpoint inhibitor (anti-PD-1 or anti-PD-L1) for the treatment of inoperable locally advanced or metastatic disease.

   - *Allowed are up to 2 lines of prior systemic anticancer therapy to treat inoperable locally advanced or metastatic UC including prior treatment with an anti-CTLA-4 agent.*
   - *Excluded are subjects who had a prior combination therapy of an ICI (anti-PD-1 or anti-PD-L1) with a VEGFR-targeting TKI.*

v. Exploratory Single-Agent Cabozantinib (SAC) Cohort 20: Subjects with Stage IV non-squamous NSCLC who have radiographically progressed on or after treatment with one prior immune checkpoint inhibitor (anti-PD-1 or anti-PD-L1) for metastatic disease.

   - *Allowed are up to 2 lines of prior systemic anticancer therapy to treat metastatic NSCLC including prior treatment with an anti-CTLA-4 agent.*
   - *Excluded are subjects who had a prior VEGFR-targeting TKI*
   - *Excluded are subjects who have been diagnosed with an EGFR sensitizing mutation, ALK rearrangement, ROS1 rearrangement, or BRAF V600E mutation.*

w. Exploratory Single-Agent Cabozantinib (SAC) Cohort 21, Exploratory Single-Agent Atezolizumab (SAA) Cohort 22, and Combination-Therapy Expansion Cohort 23: Subjects with metastatic CRPC who have histologically or cytologically confirmed adenocarcinoma of the prostate without small cell component (Note: Neuroendocrine differentiation and other histologic components are permitted if adenocarcinoma is the primary histology) with the following requirements:

   - 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 (mCSPC), M0 CRPC, or mCRPC.

     *Note: Subjects may have previously received taxane-based chemotherapy for mCSPC but no other approved or experimental nonhormonal systemic therapies for metastatic prostate cancer.*

   - Bilateral orchiectomy or ongoing androgen deprivation therapy with a GnRH agonist/antagonist (surgical or medical castration), with serum testosterone $\leq$ 50 ng/dL ($\leq$ 1.73 nmol/L) at screening.
   - Progressive disease at study entry as defined by at least one of the following two criteria:

     a. PSA progression defined by a minimum of 2 rising PSA values from 3 or 4 consecutive assessments with an interval of at least 7 days between assessments. The most recent qualifying PSA value must be drawn within 28 days of planned enrollment. (Note: If qualifying solely by PSA progression, the screening central lab PSA value must be at least 2 ng/mL [2 µg/L] but need not serve as last PSA

value for determination of PSA progression; up to one PSA decrease is permitted as long as it is not the most recent value), OR

b. Soft tissue disease progression in the opinion of the Investigator. Note: Bone disease progression alone does not qualify.

- High risk metastatic disease per Investigator read as defined by at least one of the following:

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

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

x. Combination-Therapy Expansion Cohort 24: Subjects with metastatic CRPC who have histologically or cytologically confirmed adenocarcinoma of the prostate without small cell component (Note: Neuroendocrine differentiation and other histologic components are permitted if adenocarcinoma is the primary histology) with the following requirements:

- Prior taxane-based chemotherapy initiated for mCRPC (Note: Subjects may or may not have previously received docetaxel for mCSPC.)
- Prior treatment with at least one NHT (eg, abiraterone, apalutamide, darolutamide, or enzalutamide) for castration-sensitive locally advanced (T3 or T4) or metastatic castration-sensitive prostate cancer (mCSPC), M0 CRPC, or mCRPC.
- Bilateral orchiectomy or ongoing androgen deprivation therapy with a GnRH agonist/antagonist (surgical or medical castration), with serum testosterone $\leq$ 50 ng/dL ($\leq$ 1.73 nmol/L) at screening.
- 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 consecutive assessments with an interval of at least 7 days between assessments. The most recent qualifying PSA value must be drawn within 28 days of planned enrollment. (Note: If qualifying solely by PSA progression, the screening central lab PSA value must be at least 2 ng/mL [2 µg/L] but need not serve as last PSA value for determination of PSA progression; up to one PSA decrease is permitted as long as it is not the most recent value), OR

  b. Soft tissue disease progression in the opinion of the Investigator. Note: Bone disease progression alone does not qualify.

- High risk metastatic disease per Investigator read as defined by at least one of the following:

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

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

2. Measurable disease per RECIST 1.1 as determined by the Investigator. Measurable disease must be outside the radiation field if prior radiation therapy was administered.
3. Tumor tissue material available (archival or recent tumor biopsy).

   *NOTE: Subjects in Cohorts 6 and 21-23 are exempt from this criterion if no archival tissue is available and subjects are unwilling to undergo a fresh tumor biopsy or a fresh biopsy is not safely obtainable.*
4. Recovery to baseline or ≤ Grade 1 CTCAE v4 from toxicities related to any prior treatments, unless AE(s) are clinically nonsignificant and/or stable on supportive therapy.
5. Age eighteen years or older on the day of consent.
6. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1.
7. Adequate organ and marrow function, based upon meeting all of the following laboratory criteria within 14 days before first dose of study treatment:
   a. Absolute neutrophil count (ANC) ≥ 1500/µL (≥ $1.5 \times 10^9$/L) without granulocyte colony-stimulating factor support within 2 weeks before screening laboratory sample collection.
   b. White blood cell count ≥ 2500/µL (≥ $2.5 \times 10^9$/L).
   c. Platelets ≥ 100,000/µL (≥ $100 \times 10^9$/L) without transfusion within 2 weeks before screening laboratory sample collection. For subjects with HCC ≥ 75,000/µL (≥ $75 \times 10^9$/L).
   d. Hemoglobin ≥ 9 g/dL (≥ 90 g/L) without transfusion within 2 weeks before screening laboratory sample collection.
   e. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) ≤ 3 × upper limit of normal (ULN). ALP ≤ 5 × ULN with documented bone metastases. For subjects with HCC: ALT, AST, and ALP ≤ 5 × ULN. For subjects with mCRPC with documented bone metastases: ALT ≤ 3 × ULN, AST ≤ 3 × ULN, and ALP ≤ 10 × ULN. If ALP > 5 × ULN in mCRPC subjects, then it must be demonstrated that it is predominantly bone-specific ALP.
   f. Total bilirubin ≤ 1.5 × ULN (for subjects with Gilbert's disease ≤ 3 × ULN). For subjects with HCC ≤ 2 mg/dL (≤ 34.2 µmol/L).
   g. Serum creatinine ≤ 1.5 × ULN or calculated creatinine clearance ≥ 40 mL/min (≥ 0.67 mL/sec) using the Cockcroft-Gault equation (see Table 5-2 for Cockcroft-Gault formula).
   h. Urine protein/creatinine ratio (UPCR) ≤ 1 mg/mg (≤ 113.2 mg/mmol). For subjects with UC: ≤ 2 mg/mg (≤ 226.4 mg/mmol) creatinine.
8. Capable of understanding and complying with the protocol requirements and must have signed the informed consent document.
9. 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 (defined in Appendix K) during the course of the study

and for 5 months after the last dose of study treatment. An additional contraceptive method, such as a barrier method (eg, condom), is recommended.

10. Female subjects of childbearing potential must not be pregnant at screening. Female subjects are considered to be of childbearing potential unless one of the following criteria is met: permanent sterilization (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) or documented postmenopausal status (defined as 12 months of amenorrhea in a woman over 45 years-of-age in the absence of other biological or physiological causes. In addition, females under 55 years-of-age must have a serum follicle stimulating hormone (FSH) level > 40 mIU/mL to confirm menopause). Note: Documentation may include review of medical records, medical examination, or medical history interview by study site staff.

### 4.3 Exclusion Criteria

A subject who meets any of the following criteria is ineligible for the study:

1. Prior treatment with cabozantinib or ICIs including anti-CTLA-4, anti-PD-1, anti-PD-L1, anti-PD-L2, anti-OX-40, anti-CD137 therapy except for Expansion Cohorts 5, 7, 9, 11, and 17, and SAC Cohorts 19 and 20 in which prior anti-PD-1 or anti-PD-L1 therapy is required and/or allowed for eligibility (see Inclusion Criteria 1g, 1i, 1k, 1m, 1s, 1v, and 1w, respectively, for details).
2. Receipt of any type of small molecule kinase inhibitor (including investigational kinase inhibitor) within 2 weeks before first dose of study treatment. EGFR targeted TKIs are allowed to be continued until 5 days prior to first dose of study treatment in Expansion Cohort 9.
3. For mCRPC subjects (Expansion Cohorts 6 and 23-24, Exploratory SAC Cohort 21, and Exploratory SAA Cohort 22): receipt of abiraterone within 1 week before first dose of study treatment or receipt of any other androgen-receptor inhibitors within 2 weeks before first dose of study treatment.
4. HCC subjects who meet any of the following criteria are ineligible:
    a. Received prior local anticancer therapy (including embolization and ablation) within 4 weeks before first dose of study treatment. For prior radiation for bone metastases, refer to Exclusion Criteria 6.
    b. Subjects with fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma.
5. Receipt of any type of anticancer antibody (including investigational antibody) or systemic chemotherapy within 4 weeks before first dose of study treatment except for Expansion Cohorts 5, 7, 9, 11, and 17, and SAC Cohorts 19 and 20 in which receipt of a PD-1, PD-L1, or CTLA-4 targeting antibody is permitted within 4 weeks before first dose of study treatment.
6. Radiation therapy for bone metastasis within 2 weeks, any other local radiation therapy within 4 weeks before first dose of study treatment. Subjects who have received systemic treatment with radionuclides within 6 weeks before first dose of study treatment are not eligible. Subjects with clinically relevant ongoing complications from prior radiation therapy are not eligible.

7. Known brain metastases or cranial epidural disease unless adequately treated with radiotherapy and/or surgery (including radiosurgery) and stable for at least 4 weeks before first dose of study treatment. Eligible subjects must be neurologically asymptomatic and without corticosteroid treatment at the time of first dose of study treatment.
8. Concomitant anticoagulation with oral anticoagulants 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 specified direct factor Xa inhibitors rivaroxaban, edoxaban, or apixaban in subjects (excluding HCC subjects) without known brain metastases who are on a stable dose of the anticoagulant for at least 1 week before first dose of study treatment and without clinically significant hemorrhagic complications from the anticoagulation regimen or the tumor.

            *Note: Subjects with HCC may be treated with therapeutic LMWH but must have a screening platelet count > 100,000/μL. Direct inhibitors of thrombin or factor Xa are not permitted in subjects with HCC.*
9. Diagnosis of immunodeficiency or is receiving systemic steroid therapy (> 10 mg daily prednisone equivalent) or any other form of immunosuppressive therapy within 2 weeks prior to first dose of study treatment. Inhaled, intranasal, intraarticular, and topical corticosteroids and mineralocorticoids are allowed.
   *Note: Adrenal replacement steroid doses > 10 mg daily prednisone equivalent are permitted in the absence of active autoimmune disease. Transient short-term use of systemic corticosteroids for allergic conditions (eg, contrast allergy) is also allowed.*
10. Administration of a live, attenuated vaccine within 30 days before first dose of study treatment.
11. The subject has uncontrolled, significant intercurrent or recent illness including, but not limited to, the following conditions:
    a. Cardiovascular disorders:
        i. Congestive heart failure New York Heart Association Class 3 or 4, unstable angina pectoris, serious cardiac arrhythmias.
        ii. Uncontrolled hypertension defined as sustained blood pressure (BP) > 140 mm Hg systolic or > 90 mm Hg diastolic despite optimal antihypertensive treatment.
        iii. Stroke (including transient ischemic attack [TIA]), myocardial infarction (MI), or other ischemic event, or thromboembolic event (eg, deep venous thrombosis [DVT], PE) within 6 months before first dose. Upon Sponsor approval, subjects with a diagnosis of incidental, subsegmental PE or DVT within 6 months are allowed if stable, asymptomatic, and treated with anticoagulation for at least 1 week before first dose. Iatrogenic arterial embolization procedures such as tumor arterial embolization or splenic artery embolization are allowed.

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

   i. Tumors invading the GI-tract, active peptic ulcer disease, inflammatory bowel disease, diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis or acute obstruction of the pancreatic or biliary duct, or gastric outlet obstruction. Presence of primary GI tumor is not excluded.

   ii. Abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess within 6 months before first dose. Note: Complete healing of an intra-abdominal abscess must be confirmed before first dose.

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

c. Clinically significant hematuria, hematemesis, or hemoptysis of > 0.5 teaspoon (2.5 mL) of red blood, or other history of significant bleeding (eg, pulmonary hemorrhage) within 12 weeks before first dose.

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

e. Lesion invading a major blood vessel including, but not limited to, inferior vena cava, pulmonary artery, or aorta. HCC subjects with lesions invading the hepatic portal vasculature are eligible.

f. Other clinically significant disorders such as:

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

      - A history of autoimmune-related hypothyroidism and on thyroid replacement hormone therapy

        *Note: Subjects with prior history of thyroiditis are allowed if they have undergone sub-total, near-total, or total thyroidectomy.*

      - Controlled Type 1 diabetes mellitus and on an insulin regimen
      - Asthma
      - Eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only provided all of following are true:
        - Rash covers < 10% of body surface area

- Disease is well controlled at baseline and requires only low-potency topical corticosteroids
- No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high potency or oral corticosteroids within the previous 12 months

ii. Active infection requiring systemic treatment, infection with human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness, acute or chronic hepatitis B or C infection in non-HCC tumor cohorts, or a known positive test for tuberculosis infection if supported by clinical or radiographic evidence of disease. Subjects with history of COVID-19 must have recovered from the disease at least 30 days prior to enrollment.

iii. History of idiopathic pulmonary fibrosis, organizing pneumonia (eg, bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computerized tomography (CT) scan. History of radiation pneumonitis in the radiation field (fibrosis) is permitted.

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

v. Malabsorption syndrome.

vi. For all subjects except Cohort 18 (DTC): Free thyroxine (FT4) outside the laboratory normal reference range. Asymptomatic subjects with FT4 abnormalities can be eligible after sponsor approval.

vii. Moderate to severe hepatic impairment for subjects with chronic liver disease (Child-Pugh B or C; Appendix L).

viii. Requirement for hemodialysis or peritoneal dialysis.

ix. History of solid organ or allogenic stem cell transplant.

12. Major surgery (eg, GI surgery, removal or biopsy of brain metastasis) within 4 weeks or minor surgery (eg, simple excision, tooth extraction) within 10 days before first dose of study treatment. Complete wound healing from surgery must have occurred before first dose. Subjects with clinically relevant ongoing complications from prior surgery are not eligible.
13. Corrected QT interval calculated by the Fridericia formula (QTcF) > 500 ms per electrocardiogram (ECG) within 14 days before first dose of study treatment (see Section 5.6.4 for Fridericia formula).

    *Note: If a single ECG shows a QTcF with an absolute value > 500 ms, two additional ECGs at intervals of approximately 3 min must be performed within 30 min after the initial ECG, and the average of these three consecutive results for QTcF will be used to determine eligibility (ie, if the average is ≤ 500 ms the subject is eligible).*
14. Pregnant or lactating females.
15. Inability to swallow tablets.

16. Previously identified allergy or hypersensitivity to components of the study treatment formulations. *Subjects with a history of infusion-related reaction to prior therapy with atezolizumab may be eligible by sponsor approval if the reaction was considered mild and manageable with appropriate supportive care (eg, use of premedication according to standard of care).*
17. Diagnosis of another malignancy within 2 years before first dose of study treatment, except for superficial skin cancers, or localized, low grade tumors deemed cured and not treated with systemic therapy. Incidentally diagnosed prostate cancer is allowed if assessed as stage ≤ T2N0M0 and Gleason score ≤ 6.

# 5 STUDY ASSESSMENTS AND PROCEDURES

The study assessment schedules are presented in Appendix A for the Dose-Escalation Stage, in Appendix B for the Combination-Therapy Cohorts, SAC Cohorts, and SAA Cohort in the Expansion Stage, and in Appendix C for the subjects who have Investigator-assessed radiographic progression per RECIST 1.1 in an SAC or SAA cohort and are receiving combination treatment in the Second Agent Add-On Stage.

Most study assessments and procedures (including treatment administration) will be performed in cycles. Cycle 1 Day 1 (C1D1) is defined as the date of first dose of any study treatment.

Cycles for the Dose-Escalation Stage and Combination-Therapy Cohorts in the Expansion Stage: A cycle is generally the 21-day interval starting with the date of an atezolizumab infusion and ending with the day before the next atezolizumab infusion. However, under some circumstances no atezolizumab may be dosed during a cycle:

- If atezolizumab treatment is discontinued but cabozantinib treatment is allowed to continue with the notification of the Sponsor, each consecutive 21-day interval starting with the date of the decision to discontinue atezolizumab will be defined as a cycle. If the decision to discontinue atezolizumab occurs less than 21 days after the last infusion, then the next cycle will begin on the 22$^{nd}$ day after the last infusion.

Cycles may extend beyond 21 days if atezolizumab dosing is delayed. During an atezolizumab dose delay, subjects should return to the site for scheduled safety visits every three weeks from the last dose of atezolizumab. Further, the study site should perform unscheduled visits or telephone calls weekly (or more frequently) as clinically indicated to monitor subject safety and appropriateness for re-treatment with study treatment.

Cycles for the Exploratory SAC Cohorts: The first cycle is the 21-day interval starting with the date of first dose of cabozantinib treatment. Subsequent cycles will each be exactly 21 days long, irrespective of whether cabozantinib treatment is being interrupted at the end of the cycle.

Cycles for the Exploratory SAA Cohort: A cycle is generally the 21-day interval starting with the date of an atezolizumab infusion and ending with the day before the next atezolizumab infusion.

Cycles for the Second Agent Add-On Stage: A cycle is generally the 21-day interval starting with the date of an atezolizumab infusion and ending with the day before the next atezolizumab infusion. For subjects on the SAA Cohort, the first dose of cabozantinib must be taken on an atezolizumab dosing day. As with the Combination-Therapy Cohorts in the Expansion Stage,

there are some circumstances under which no atezolizumab may be dosed during a cycle (see above for details). The first day of the Second Agent Add-On Stage will occur on the first day the second agent (ie, atezolizumab for the SAC Cohorts and cabozantinib for the SAA Cohort) is administered. That date will be designated as Add-On Cycle 1 Day 1 (aoC1D1).

Imaging Schedule: Imaging assessments (CT, magnetic resonance imaging [MRI], bone scan) are to be performed at protocol-defined intervals based on the first dose of study treatment (defined as Week 1 Day 1 [W1D1]); all subsequent time points for these assessments will apply the same nomenclature, which will not be modified as a result of modifications or discontinuations of treatment administration. The frequencies of imaging assessments are provided in Appendix A for the Dose-Escalation Stage, in Appendix B for the Combination-Therapy Cohorts, SAC Cohorts, and SAA Cohort in the Expansion Stage, and in Appendix C for the Second Agent Add-On Stage.

Considerations for Maintaining Assessment Schedules:

Unless otherwise indicated, in the absence of toxicity all scheduled visits will occur within windows for the protocol-specified visit schedule. If the subject experiences toxicity, study treatment can be modified or delayed as described in Section 6.5. If the subject is unable to have a study assessment taken within the defined time window due to an event outside of his or her control (eg, clinic closure, personal emergency, inclement weather, vacation), the assessment should be performed as close as possible to the required schedule. Special accommodations during the global COVID-19 pandemic are described in Appendix M. Laboratory panels for serum chemistry, hematology, and urinalysis are defined in Section 5.6.5.

## 5.1 Pretreatment 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 Institutional Review Board (IRB)/ Ethics Committee (EC) policies. Informed consent may be obtained greater than 28 days before first dose of study treatment. At informed consent, subjects will be assigned a 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 (Dose-Escalation Stage) and Appendix B (Combination-Therapy Expansion Cohorts, SAC Cohorts, and SAA Cohort) and as described in Section 5.6. Qualifying screening assessments must be performed within 28 days before the first dose of study treatment unless otherwise stated (certain lab values must be obtained closer to first dose of study treatment). Eligibility criteria based on laboratory values will use the central laboratory result (except serum pregnancy test and 24-hour urine protein; see Section 5.6.5). Local laboratory assessments may be obtained and used if the results are required by the investigator in a rapid timeframe to confirm eligibility. Local laboratory results used for confirmation of eligibility 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.

## 5.2 Treatment Period

While the subject is receiving study treatment, the subject's clinical status is to be evaluated by an Investigator at each clinic visit to confirm that the subject is suitable for continuing study treatment and to make timely decisions regarding the interruption or restarting of study treatment. Clinical laboratory results from samples obtained during clinic visits and tumor assessments from imaging visits are to be reviewed by an Investigator. Also refer to Section 5.6.5 for handling of samples for laboratory assessments.

Subjects will receive study treatment as long as they continue to experience clinical benefit in the opinion of the investigator or until unacceptable toxicity, the need for subsequent systemic anticancer treatment, or until any other reasons for treatment discontinuation listed in the protocol (Section 3.8). Administration of study treatment may continue after radiographic progression per RECIST 1.1 as long as subjects meet all of the following criteria:

- Evidence of clinical benefit, as determined by the investigator following a review of all available data
- Absence of symptoms and signs indicating unequivocal progression of disease (eg, laboratory values, such as clinically significant hypercalcemia for subjects with RCC) that cannot be managed by optimizing supportive therapy
- Absence of decline in ECOG performance status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (eg, leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions.

Subjects on single-agent treatment in the SAC and SAA Cohorts may continue to receive single-agent treatment after they have radiographically progressed per RECIST 1.1 if they meet the above criteria. In order to begin combination treatment in the Second Agent Add-On Stage, these subjects must meet the eligibility criteria in Appendix C (see Section 3.5.2.4).

The investigator should take into consideration the possibility of a delayed anti-tumor immune response with the possibility of regressing and enlarging tumor lesions at the same imaging time point (mixed response) or the appearance of new lesions prior to achieving a radiological response.

Clinic visits for safety evaluations will occur at minimum every 3 weeks (± 3 days) after treatment is initiated independent of any dose delays or interruptions. The final assessment will occur at the Post-Treatment Follow-Up Visit unless an AE is determined to be ongoing (see Section 5.3).

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

Radiographic tumor assessments will be performed as described in Section 5.6.9. The schedule of assessments should be followed regardless of whether study treatment is reduced, interrupted, delayed, or discontinued.

### 5.2.1 Dose-Escalation Stage (Combination Therapy)

In the Dose-Escalation Stage, cohorts will be defined by the starting dose-level of cabozantinib evaluated and the schedule of the first infusion of atezolizumab (either on C1D1 with the first dose of cabozantinib or on C2D1, 21 days after the first dose of cabozantinib; see Section 3.5.1). Eligible subjects will be enrolled in the open cohort, irrespective of tumor type. Subjects in the Dose-Escalation Stage will be treated and evaluated according to the schedule of assessments provided in Appendix A.

### 5.2.2 Expansion Stage

Subjects in the Expansion Stage will be assigned to a treatment cohort based on tumor type and prior cancer history as described in Section 3.5.2.

#### 5.2.2.1 Combination-Therapy Cohorts

The cabozantinib starting dose level defined by the Cohort Review Committee in combination with atezolizumab will be administered to the initially enrolled subjects in the Expansion Cohorts and any additional subjects enrolled per Extended Enrollment Option 1. Additional

subjects enrolled per Extended Enrollment Option 2 will receive cabozantinib 60 mg in combination with the standard dose of atezolizumab. For details on the Extended Enrollment Options, see Section 3.5.2.1.

Study treatment will be administered according to the Cohort Review Committee-recommended dosing schedule. Expansion Cohort subjects will be evaluated according to the scheduled of assessments provided in Appendix B.

#### 5.2.2.2 Exploratory Single-Agent Cabozantinib (SAC) Cohorts

Three SAC Cohorts 19, 20, and 21 will enroll UC subjects, NSCLC subjects, and CRPC subjects, respectively. Subjects enrolled in SAC Cohorts will receive single-agent cabozantinib 60 mg as the initially assigned dosing regimen. Subjects in the SAC Cohorts will be evaluated according to the schedule of assessments provided in Appendix B.

#### 5.2.2.3 Exploratory Single-Agent Atezolizumab (SAA) Cohort

SAA Cohort 22 will enroll CRPC subjects. Subjects enrolled in this cohort will receive single-agent atezolizumab 1200 mg IV, q3w and be evaluated according to the schedule of assessments provided in Appendix B.

#### 5.2.2.4 Second Agent Add-On Stage (For Subjects Enrolled in Single-Agent Cohorts)

Subjects enrolled into SAA or SAC cohorts 19, 20, 21, or 22 may have the option to be treated with combination therapy (cabozantinib and atezolizumab) after Investigator-assessed radiographic progression per RECIST 1.1 following treatment with single-agent therapy. After signing their consent, subjects who transition to combination treatment in the Second Agent Add-On Stage will receive atezolizumab doses of 1200 mg IV q3w and cabozantinib doses at the lower of 40 mg PO qd or their most recently received dose level (see Section 3.5.2.4 for details). Eligibility criteria and the schedule of assessments for the Second Agent Add-On Stage are presented in Appendix C.

### 5.3 Post-Treatment Period

Subjects who discontinue from study treatment will return to the site 30 days (+ 14 days) after the date of the decision to discontinue study treatment for a Post-Treatment Follow-Up Visit. During the Post-Treatment Follow-Up Visit, safety assessments will be performed. Refer to Appendix A (Dose-Escalation Stage), Appendix B (Combination-Therapy Expansion Cohorts, SAC Cohorts, and SAA Cohort), or Appendix C (Second Agent Add-On Stage) for a description of all assessments for the Post Treatment Follow-Up Visit.

The date of the decision to discontinue study treatment is defined for each subject as the later of (a) the date of the decision of the Investigator to permanently discontinue study treatment or (b) the date of the last dose of study treatment taken by the subject.

Adverse events (including irAEs and AESIs) are to be documented and/or followed as described in Section 8.4.

Subjects will be followed for OS as described in Section 5.6.11. Receipt of nonprotocol anticancer therapy will be collected during survival follow-up. If a subject is lost to follow-up, multiple attempts to contact the study subject or designee must be documented in the subject records.

Radiographic tumor assessments may need to be collected until radiographic progression as described in Section 5.6.9.

These assessments in the Post-Treatment Period (including the Post-Treatment Follow-Up Visit) are not required for subjects who discontinue study treatment in the Maintenance Phase (such subjects are to be followed per standard of care).

## 5.4 Maintenance Phase

The purpose of the Maintenance Phase is to continue to provide long-term access to study drug(s) to subjects who are deriving clinical benefit even after evaluation of the study objectives has been completed. When sufficient data have been collected to adequately evaluate all study endpoints, and upon site notification by the Sponsor, subjects who continue study treatment or who have not completed the Post-Treatment Follow-Up Visit will enter the study Maintenance Phase. Upon initiation of the Maintenance Phase, the Sponsor considers the safety and efficacy profile of the drug within this study to have been sufficiently established for regulatory purposes. After implementation of the Maintenance Phase, the study will be considered complete at sites and in countries that no longer have active subjects.

In the Maintenance Phase, subjects who remain on treatment will continue to receive study treatment until a criterion for protocol-defined discontinuation has been met (Section 3.8). Subjects are to undergo periodic safety assessments (including local laboratory tests) and tumor assessments (Appendix D). The nature and frequency of these assessments are to be performed per standard of care if allowed per local regulations. It is the Investigator's responsibility to ensure that subject visits occur frequently enough and adequate assessments are performed to ensure subject safety.

Subjects who enter the Maintenance Phase after discontinuing study treatment, but prior to their Post-Treatment Follow Up Visit, are to be followed in the Maintenance Phase until their Post-Treatment Follow Up Visit.

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

Further, the following AEs (including irAEs), 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 (including irAEs), whether serious or not, leading to study treatment discontinuation
- Adverse events (including irAEs), 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 6.4.

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

## 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. The laboratory assessments will be done by the central lab; however, if the results are needed immediately (eg, for AE management), they may be done by the local lab and the results forwarded to the management vendor for handling of local laboratory data. Whenever possible a sample for central lab analysis will also be collected. During a dose interruption due to AE (ie, the time between the last dose and the time drug is restarted), the study site should perform unscheduled visits or telephone calls weekly (or more frequently) as clinically indicated to monitor subject safety and appropriateness for re-treatment with study treatment.

## 5.6 Procedure Details

### 5.6.1 Demographics, Medical and Cancer History

Demographics at screening will include age at informed consent, medical and cancer history (including PSA doubling time [PSADT] for CRPC subjects), surgical history, radiation therapy

history, and systemic anticancer treatment history including names of agents and administration dates. Refer to Appendix A for the schedule of these assessments for the Dose-Escalation Stage and Appendix B for the Combination-Therapy Expansion Cohorts, SAC Cohorts, and SAA Cohort.

### 5.6.2 Physical Examination

Physical examinations at screening will include height, weight, performance status, and an assessment of the following systems: skin, head, eyes, ears, nose, throat, respiratory system, cardiovascular system, GI system, neurological condition, blood and lymphatic systems, and the musculoskeletal system. Symptom-directed physical examination will be conducted on C1D1 before the first dose of study treatment and at subsequent safety assessment visits. Any ongoing / intercurrent condition(s) prior to first dose will be recorded in source documents and on case report forms (CRFs).

The Karnofsky performance status will be assessed during screening for subjects with RCC to determine the prognostic risk score according to the MSKCC prognostic criteria (Motzer et al 2004). For all subjects the ECOG performance status will be assessed at screening and at subsequent visits. A table for both performance status scores is included in Appendix F for reference.

Refer to Appendix A for the schedule of physical examination and performance status assessments for the Dose-Escalation Stage and Appendix B for the Combination-Therapy Expansion Cohorts, SAC Cohorts, and SAA Cohort. Refer to Appendix C for the schedule of physical examination and performance status assessments for subjects in the Second Agent Add-On Stage.

### 5.6.3 Vital Signs

Vital signs including approximately 5-minute sitting BP, pulse, respiratory rate, and temperature will be assessed at the time points indicated in Appendix A (Dose-Escalation Stage), Appendix B (Combination-Therapy Expansion Cohorts, SAC Cohorts, and SAA Cohort in the Expansion Stage), and Appendix C (Second Agent Add-On Stage). 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.

### 5.6.4 Electrocardiogram 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 the single ECG shows a QTcF with an absolute value > 500 ms, two additional ECGs at intervals of approximately 3 min must be performed within 30 min after the initial ECG, and the average of these three consecutive results for QTcF will be used (see Section 6.5.2.1.15).

ECGs will be performed at the time points indicated in Appendix A (Dose-Escalation Stage), Appendix B (Combination-Therapy Expansion Cohorts, SAC Cohorts, and SAA Cohort), and Appendix C (Second Agent Add-On Stage).

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

The Fridericia formula is depicted below for calculation of QTcF.

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

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

### 5.6.5 Laboratory Assessments

Laboratory analytes that will be measured for this study are listed in Table 5-1. The schedule for laboratory assessments is provided in Appendix A for the Dose-Escalation Stage, Appendix B for the Combination-Therapy Expansion Cohorts, SAC Cohorts, and SAA Cohort, and in Appendix C for the Second Agent Add-On Stage. Laboratory tests to establish eligibility must be done within 14 days prior to first dose of study treatment unless otherwise stated.

Hematology, serum chemistry, coagulation, UPCR including components, and thyroid function tests are to be performed by a central laboratory for samples collected at scheduled safety visits and at unscheduled visits whenever possible. All central laboratory results will be provided to the investigator. Local laboratory assessments for these panels may be obtained and used if the results are required by the investigator in a rapid timeframe. All local laboratory results must be forwarded to the study local laboratory management vendor if performed in lieu of the central laboratory assessment at any scheduled or unscheduled visit.

Routine (dipstick) urinalysis, microscopic urine examination, and serum and urine pregnancy tests are to be performed by a local laboratory. Results or status from these tests will be recorded on CRFs and will not be submitted to the study local laboratory management vendor.

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

Serum chemistry, hematology, and urinalysis laboratory samples must be collected and the results must be reviewed within 72 h before any atezolizumab infusion administered on study.

Throughout the study, glucose is to be monitored (no caloric intake for at least 8 hours, consumption of water is allowed).

A serum pregnancy test must be repeated before dosing on C1D1 unless a pregnancy evaluation was done during screening within 7 days prior to C1D1. Pregnancy tests (serum or urine) will be performed for post-baseline pregnancy evaluations.

Follicle stimulating hormone will be assessed during screening for women under the age of 55 years to confirm menopause (see Inclusion Criterion #10 in Section 4.2).

For all tumor types except HCC: Hepatitis B surface antigen and Hepatitis C antibody (with reflex testing of Hepatitis C virus RNA if antibody test is positive) will be assessed at screening.

For HCC subjects: Hepatitis B surface antigen, Hepatitis B core antibody, Hepatitis B e-antigen/e-antibody, Hepatitis B DNA, Hepatitis D testing for Hepatitis B positive, Hepatitis C antibody, and Hepatitis C virus RNA will be assessed at screening.

For CRPC subjects: Serum testosterone will be assessed at screening.

Additional tumor markers will be assessed for selected tumor indications: PSA for CRPC, CA125 for OC, AFP for HCC, CEA for CRC, and thyroglobulin for DTC. Subjects with these tumor types will have the corresponding tumor markers assessed at screening and after first dose of study treatment as described in Section 5.6.9.4 and the schedule of assessments for the Combination-Therapy Expansion Cohorts, SAC Cohorts, and SAA Cohort in the Expansion Stage (Appendix B), and for subjects in the SAC and SAA cohorts who have radiographically progressed per RECIST 1.1 on single-agent treatment and are receiving combination treatment in the Second Agent Add-On Stage (Appendix C).

## Table 5-1: Clinical Laboratory Panels

**Central Laboratory**

*If performed by local laboratory in lieu of central lab assessment, submit results to study local laboratory management vendor*

| Laboratory Assessments for All Cohorts | | Cohort-Specific Assessments |
|---|---|---|
| **Hematology:**<br>• White blood cell (WBC) count with differential (ANC, basophils, eosinophils, lymphocytes, monocytes)<br>• hematocrit<br>• platelet count<br>• red blood cell count<br>• hemoglobin<br><br>**Coagulation:**<br>• prothrombin time (PT)/International Normalized Ratio (INR)<br>• partial thromboplastin time (PTT)<br><br>**Thyroid function:**<br>• thyroid-stimulating hormone (TSH)<br>• Free thyroxine (T4; required at screening; after screening only if TSH is outside normal range)<br><br>**Urine Chemistry:**<br>• Protein (spot urine; fully quantitative)<br>• Creatinine (spot urine; fully quantitative)<br>• Urine protein/creatinine ratio (UPCR; spot urine) | **Serum Chemistry**<br>• albumin<br>• total alkaline phosphatase (ALP)<br>• amylase<br>• alanine amino transferase (ALT)<br>• aspartate amino transferase (AST)<br>• blood urea nitrogen (BUN)<br>• corrected calcium<br>• bicarbonate<br>• chloride<br>• creatinine<br>• γ-glutamyltranspeptidase (GGT)<br>• glucose<br>• lactate dehydrogenase (LDH)<br>• lipase<br>• magnesium<br>• phosphorus<br>• potassium<br>• sodium<br>• total bilirubin (conjugated and unconjugated if total bilirubin elevated)<br>• total protein<br><br>**Hepatitis screening (All Non-HCC Cohorts):**<br>• Hepatitis B surface antigen (HBsAg; screening)<br>• Hepatitis C virus antibody (HCV Ab; HCV RNA reflex testing if antibody positive [screening])<br><br>**Other Parameters**<br>• Follicle Stimulating Hormone (FSH)[a] | **CRPC Cohorts 6 and 21-24:**<br>• Testosterone (serum, baseline only)<br>• Prostate-specific antigen (PSA)<br>• Bone-specific ALP<br><br>**Ovarian Cancer Cohort 12:**<br>• CA125<br><br>**HCC Cohort 14:**<br>• Alpha-fetoprotein (AFP)<br>• Screening assessments:<br>• Hepatitis Viral assessments:<br>o Hepatitis B surface antigen (HBsAg)<br>o Hep B core antibody<br>o Hep B e-antigen/e-antibody<br>o HBV DNA<br>o Hepatitis C virus antibody (HCV Ab)<br>o Hep C viral load (PCR)HDV testing for HBV positive<br><br>**CRC Cohort 16**<br>• Carcinoembryonic antigen (CEA)<br><br>**DTC Cohort 18**<br>• Thyroglobulin |

CRPC, castration-resistant prostate cancer; DTC, differentiated thyroid cancer; HCC, hepatocellular cancer.

| Local Laboratory (All Cohorts)<br>*Submit only 24-hour urine protein test results to study local laboratory management vendor* | | |
|---|---|---|
| **Urinalysis**<br>(Dipstick or Routine as per institutional standard)<br>• pH<br>• specific gravity<br>• ketones<br>• protein<br>• glucose<br>• nitrite<br>• urobilinogen<br>• leukocyte esterase<br>• blood | **Microscopic Urine Examination**<br>• Perform at the discretion of the investigator based on results or routine urinalysis or as clinically indicated<br><br>**Urine Chemistry**<br>• 24-hour urine protein: perform at the discretion of the investigator based on increases in UPCR from routine assessments | **Pregnancy Blood Test (prior to first dose)**<br>• β-human chorionic gonadotropin (β-HCG)<br><br>**Pregnancy Urine or Blood Test (after first dose of study treatment)**<br>• β-human chorionic gonadotropin (β-HCG) |

[a] For women under the age of 55 years to confirm menopause as needed. Local laboratory tests can be used, if necessary.

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

***Based on Serum creatinine in conventional units (mg/dL)***

- Males: (140 – age) x weight (kg)/(serum creatinine × 72)
- Females: [(140 – age) x weight (kg)/(serum creatinine × 72)] × 0.85

***Based on Serum creatinine in SI units (µmol/L)***

- Males: [(140 – age) x weight (kg)/(serum creatinine)] × 1.23
- Females: [(140 – age) x weight (kg)/(serum creatinine)] × 1.04

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

### 5.6.6 Pharmacokinetic Assessments

Unless otherwise approved by the Sponsor, PK blood samples will be obtained from all enrolled subjects as described in Section 5.6.6.1 as well as in Appendix A for the Dose-Escalation Stage and in Appendix B for the Combination-Therapy Expansion Cohorts, SAC Cohorts, and SAA Cohort. Subjects in the Second Agent Add-On Stage will no longer undergo PK assessments.

#### 5.6.6.1 Pharmacokinetic Blood Samples

Samples will be collected for the evaluation of cabozantinib and atezolizumab PK. The plasma concentrations of cabozantinib and serum concentration of atezolizumab will be measured, and the results will be used to confirm exposure to cabozantinib and atezolizumab, to identify possible drug-drug interactions between cabozantinib and atezolizumab, and to further characterize the PK for cabozantinib in these populations. Collection of PK samples may be halted early or sampling frequency may be modified at the discretion of the Sponsor.

**Dose-Escalation Stage (Combination Therapy)**:

Blood samples for PK analysis will be obtained on the date of first dose of study treatment (C1D1; prior to study treatment administration [cabozantinib and atezolizumab], approximately 5 min after completion of the atezolizumab infusion, and at 2 h, 4 h, and 6-8 h after cabozantinib dosing), and prior to study treatment dosing on C1D10, C2D1, and C3D1.

**Expansion Stage**

Combination-Therapy Expansion Cohorts:

Blood samples for PK analysis will be obtained on the date of first dose of study treatment (C1D1; prior to study treatment administration [cabozantinib and atezolizumab], approximately 5 min after completion of the atezolizumab infusion, and 2 h after the first dose of cabozantinib) and prior to study treatment dosing on C2D1 and C3D1.

**Exploratory SAC Cohorts**:

Blood samples for cabozantinib PK analysis will be obtained on the date of first dose of study treatment (C1D1; prior to cabozantinib administration) and on C2D1 and C3D1. Only the PK of cabozantinib will be assessed for subjects in the SAC Cohorts.

**Exploratory SAA Cohort**:

Blood samples for atezolizumab PK analysis will be obtained on the date of first dose of study treatment (C1D1; prior to atezolizumab administration) and approximately 5 min after completion of the atezolizumab infusion and prior to study treatment (atezolizumab infusion) dosing on C2D1 and C3D1. Only the PK of atezolizumab will be assessed for subjects in the SAA Cohort.

**Second Agent Add-On Stage**:

Pharmacokinetic assessments will not be performed once eligible subjects transition to the Second Agent Add-On Stage.

For details refer to Appendix A for the schedule of these assessments for the Dose-Escalation Stage and Appendix B for the Combination-Therapy Expansion Cohorts, SAC Cohorts, and SAA Cohort.

### 5.6.7 Immunogenicity Assessments

Blood samples will be obtained from all subjects in the combination treatment cohorts and the SAA Cohort in the Expansion Stage for immunogenicity assessment predose on C1D1, C3D1, C7D1, and at the Post-Treatment Follow-up Visit.

For subjects who radiographically progress per RECIST 1.1 on single-agent therapy in the SAC Cohorts and transition to combination therapy, blood samples for immunogenicity assessments will be collected predose on Add-On Cycle 1 Day 1 (aoC1D1), aoC3D1, and aoC7D1 in the Second Agent Add-On Stage and at the Post Treatment Follow-up Visit. For subjects who radiographically progress per RECIST 1.1 on single-agent therapy in the SAA Cohort and transition to combination therapy, a blood sample for immunogenicity assessment will be collected at the Post Treatment Follow-up Visit.

### 5.6.8 Biomarker Assessments

Blood and tissue samples will be obtained from consented subjects for analysis of established and/or exploratory biomarkers. Refer to Appendix A for the schedule for these assessments for the Dose-Escalation Stage, Appendix B for the Combination-Therapy Expansion Cohorts, SAC Cohorts, and SAA Cohort in the Expansion Stage, and Appendix C for subjects in the SAC and SAA cohorts who have radiographically progressed per RECIST 1.1 on single-agent treatment and are receiving combination treatment in the Second Agent Add-On Stage.

The required and optional blood samples will be used to study plasma, serum, and cellular biomarkers. Archival and optional fresh tumor tissue samples will be used to evaluate changes in biomarker expression and genetic/genomic alterations. The analyses will help identify biomarkers that are predictive of response to the study drug, and may help improve understanding of tumor development, tumor microenvironment and effects on peripheral immune activity for the study indications. If tumor biopsies are to be performed prior to first dose of study treatment, cabozantinib treatment will not be given until complete wound healing has occurred; if optional tumor biopsies are to be performed after first dose, cabozantinib treatment must be interrupted for

at least 5 days before optional tumor biopsies are performed and may not be reinitiated until adequate wound healing has occurred.

Analyses may include, but may not be limited to, sequencing of DNA and/or RNA from tissue and/or blood (plasma) to look for genetic/genomic changes (eg, mutations, copy number variation, mutational burden), immunohistochemical (IHC) assessment of biomarker levels in tissue (eg, MET, AXL, PD-L1), and immune cell profiling by fluorescence-activated cell sorting (FACS) analyses. These studies may use conventional as well as novel technology or methodology. The goal is to correlate modulation of these putative biomarkers to clinical outcome as a consequence of cabozantinib and atezolizumab treatment. The determination of PD-L1 levels is for research/exploratory purposes in this study and will not be shared with investigators as these results will not impact therapeutic decisions. The only exception is for NSCLC subjects in Cohort 8 for which PD-L1 level is required to be considered for enrollment. Immune cell profiling by FACS may be conducted at selected sites.

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

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

For NSCLC subjects, available tumor mutation analysis reports (indicating EGFR status) should be provided at screening. For eligibility review for Expansion cohort 8, prior PD-L1 reports from tests using the FDA approved pharmDx PD-L1 22C3 kits should be provided early in screening.

Please refer to Exelixis Pharmacokinetic and Pharmacodynamic/Biomarker Laboratory Manual for specific instructions on sample collection, processing, storage, and shipment.

### 5.6.9 Tumor Assessment

#### 5.6.9.1 Routine Tumor Assessment

Determination of the study endpoints of ORR, DOR, and PFS will be based on tumor assessment by the investigator per RECIST 1.1 (Appendix G). Additional exploratory efficacy evaluation of immune-related response will include the application of irRECIST (Appendix H). Independent review of tumor assessments may be requested at the discretion of the study sponsor; this would

potentially include submission of all radiographic images from the study (eg, CT/MRI, technetium bone scans) to an independent radiology core laboratory.

Radiographic tumor assessments will include the following (see Table 5-3 for a summary of required tumor assessments by indication):

1. **Chest / Abdomen / Pelvis / Neck:** Unless otherwise described, CT of Chest/Abdomen/Pelvis (CAP) or CT chest and MRI of abdomen/pelvis will be performed in all subjects at screening and every 6 weeks (± 5 days) after initiation of study treatment throughout the first 12 months on study. Upon completion of 12 months on study, these assessments will be performed every 12 weeks (± 7 days). For subjects with DTC and head & neck cancer, CT/MRI of the neck will be performed in addition to the CAP assessments. Subjects with head & neck cancer will be using the same imaging schedule after screening. For subjects with DTC the imaging frequency after screening will be every 9 weeks after initiation of study treatment throughout the first 12 months on study; upon completion of 12 months on study, these assessments will be performed every 12 weeks (± 7 days).

2. **Brain:** MRI (or CT) of the brain will be performed at screening in all subjects with RCC, H&N cancer, and NSCLC and for subjects with other tumor indications who have a history or clinical symptoms of brain metastasis. After study treatment initiation MRI (or CT) scans of the brain are only required in subjects with documented, treated brain metastasis or if clinically indicated by signs and symptoms suggestive of new central nervous system (CNS) metastases. Assessments after the first dose of study treatment will be performed every 12 weeks (± 7 days). MRI is the preferred imagining method for brain. If CT of the brain is performed instead of MRI, ambiguous results must be confirmed by MRI unless contraindicated. Subjects without documented brain metastasis during the screening assessment are not required to undergo brain imaging after initiating study treatment unless clinically indicated. In order to meet the eligibility requirements of the study, brain metastasis must have been treated and stable for at least 4 weeks before the first dose of study treatment.

3. **Bone scans**: Technetium bone scans (TBS) will be performed at screening in all subjects with CRPC and for subjects with other tumor indications who have a history or clinical symptoms (ie, bone pain) of bone metastases. After study treatment initiation bone scans are only required in subjects with documented bone lesions or if clinically indicated by signs and symptoms suggestive of new bone metastases. Assessments after the first dose will follow

routine clinical practice (approximately every 12 weeks throughout the first 12 months and every 24 weeks thereafter). Lesions identified on bone scan are not to be recorded as target, non-target, or new lesions. Bone scan findings alone cannot be used for the determination of progression or response in this study and need to be corroborated by CT/MRI. Bone lesions corroborated by CT/MRI must be reported as non-target or new lesions. PET scan or plain films are not considered adequate imaging techniques to measure bone lesions.

**Table 5-3: Tumor Assessment Requirements by Indication**

| Tumor Assessment | Screening | Post-Baseline |
|---|---|---|
| Chest/Abdomen/Pelvis CT[a] | All subjects | All Subjects |
| Neck CT/MRI | H&N cancer, DTC | H&N cancer, DTC |
| Brain MRI (or CT) | RCC, H&N, and NSCLC<br>For other cohorts: subjects with history or clinical symptoms of brain metastases | Subjects with documented brain metastases or clinical symptoms of new brain metastases |
| Bone Scans | CRPC<br>For other cohorts: subjects with history or clinical symptoms of bone metastases | Subjects with documented bone lesions or clinical symptoms of new bone metastases |

CRPC, castration-resistant prostate cancer; CT, computed tomography; DTC, differentiated thyroid cancer; H&N, head and neck cancer; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma.

[a] CT of chest and MRI of abdomen/pelvis is also permitted.

If there is clinical concern regarding the administration of any contrast, then a non-contrast CAP imaging study may be acceptable as a screening assessment if it clearly demonstrates measurable disease per RECIST 1.1 that can be followed without the need for contrast. In these subjects a post-contrast MRI of the brain must still be performed if required per protocol for the corresponding tumor indication to exclude new metastasis during screening. If at a follow up imaging time point the use of contrast is prohibited (eg, due to acquired impaired renal function) then the same modality should be used without contrast. Low dose non-contrast CT images from combined positron emission tomography/computed tomography (PET/CT) imaging cannot be used for tumor evaluations in this study.

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 (see Section 3.8). Treatment may continue after radiographic

progression as long as the investigator believes that the subject is still receiving clinical benefit from study treatment and that the potential benefit of continuing study treatment outweighs potential risk. Clinical judgment should be used for allowing treatment beyond radiographic progression. Subjects with clinically significant symptomatic deterioration at the time of radiographic progression may not be suitable for further treatment. Subjects enrolled in the SAC or SAA cohorts who experience Investigator-assessed radiographic progression per RECIST 1.1 may be eligible to receive the combination therapy in the Second Agent Add-On Stage (see Section 3.5.2.4 for more details). A new baseline tumor status will be established for these subjects based upon their most recent set of scans performed prior to receiving the first dose of the second agent in the Second Agent Add-On Stage; if these scans were taken > 4 weeks prior to first dose of the second agent, new scans will be required to establish the baseline.

Guidance on study treatment continuation or termination of tumor assessment based on subject status is provided in Table 5-4.

**Table 5-4: Criteria for Discontinuing Radiographic Assessments:**

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

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

[a] Investigator-assessed rPD only. Receipt of NPACT is a requirement for study treatment discontinuation (see Section 3.8).

[b] Bone scan evaluations will end on the date of last CT/MRI scan. If the bone scan schedule does not coincide with the last CT/MRI scan, no additional bone scan is needed after the last CT/MRI scan has been performed.

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

Refer to Appendix A for the schedule for these assessments for the Dose-Escalation Stage; Appendix B for the Combination-Therapy Expansion Cohorts, SAC Cohorts, and SAA Cohort in the Expansion Stage; and Appendix C for subjects in the SAC and SAA cohorts who have radiographically progressed per RECIST 1.1 on single-agent treatment and are receiving combination treatment in the Second Agent Add-On Stage.

#### 5.6.9.2 Confirmation of Tumor Response and Tumor Progression

For subjects with an overall response of PR or CR per RECIST 1.1 at a given time point, changes in tumor measurements must be confirmed by repeat assessments to be performed no fewer than 4 weeks after the criteria for response are first met. This may be performed at the next scheduled 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 ≥ 4 weeks after the initial PD criteria were met. Continuation of study treatment after confirmatory tumor imaging is at the discretion of the investigator. For subjects who continue treatment after the confirmatory tumor imaging, regularly scheduled imaging will continue.

#### 5.6.9.3 Serum Testosterone Assessment

For subjects with CRPC, serum testosterone will be determined at screening.

#### 5.6.9.4 Tumor Marker Assessment

For subjects with CRPC, HCC, OC, CRC, and DTC, tumor marker samples (ie, PSA, AFP, CA125, CEA, and thyroglobulin, respectively) will be collected at screening, Day 1 of every third cycle (or every 9 weeks, whichever is earlier) for the first 12 months, and then Day 1 of every fifth cycle (or every 15 weeks, whichever is earlier) until the earlier of initiation of subsequent systemic anticancer therapy or permanent loss to radiographic follow-up (including hospice admission).

For subjects with CRPC who receive combination treatment in the Second Agent Add-On Stage, PSA samples will be collected at screening for that stage, Day 1 of every third cycle on that stage (or every 9 weeks, whichever is earlier) for the first 12 months, and then Day 1 of every fifth cycle of that stage (or every 15 weeks, whichever is earlier) until the earlier of initiation of subsequent systemic anticancer therapy or permanent loss to radiographic follow-up (including hospice admission).

The tumor marker assessments will not be used to determine progressive disease or to make study treatment decisions in this study.

### 5.6.10 Subject Daily Dosing Diary

Subjects in the Dose-Escalation Stage will be provided a daily dosing diary with instructions to record cabozantinib treatment taken outside the clinic during the DLT Evaluation Period.

For subjects on the Standard Dosing Schedule, the diary will be initially distributed on C1D1, and it will be collected at the beginning of Cycle 2.

The daily diary is not a CRF. The diary will serve as source documentation and be maintained with other subject clinical source documents. Study site staff should carefully review the diary with the subject and to ensure it is complete and accurate before transcription to the subject's CRFs.

### 5.6.11 Overall Survival

Following study treatment discontinuation each subject will continue to be followed for survival and subsequent anticancer treatment. The investigator (or designee) will make contact (eg, in person or by telephone) with the subject at least as frequently as every 12 weeks (± 14 days) after the Post-Treatment Follow-Up Visit until the subject expires or the Sponsor decides to discontinue collection of these data for the study.

At each contact, the investigator (or designee) will determine if the subject is alive and collect information on nonprotocol anticancer treatments 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 cut-off). 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 allowed by local laws and regulations).

Refer to Appendix A for the schedule for these assessments for the Dose-Escalation Stage, Appendix B for the Combination-Therapy Expansion Cohorts, SAC Cohorts, and SAA Cohort, and Appendix C for the Second Agent Add-On Stage.

These assessments are not required for subjects who discontinue study treatment in the Maintenance Phase (such subjects are to be followed per standard of care).

# 6 TREATMENTS

## 6.1 Composition, Formulation, and Storage

At study sites, all study medication will be stored as described in the appropriate prescribing information for that country (if applicable) or the pharmacy manual and inventoried in accordance with applicable state and federal regulations.

### 6.1.1 Investigational Treatment: Cabozantinib

The Sponsor will provide each investigator with adequate supplies of cabozantinib, which will be supplied as 60-mg and 20-mg yellow film-coated tablets. The 60-mg tablets are oval and the 20-mg tablets are round. Doses of 40 mg will comprise two 20-mg tablets. The components of the tablets are listed in Table 6-1.

**Table 6-1: Cabozantinib Tablet Components and Composition**

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

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

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

### 6.1.2 Single-Agent or Combination Treatment: 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. Solution used as diluent (0.9% NaCl) should be sourced by investigative sites if available and permitted by local regulations.

### 6.2 Schedule of Treatment

Cabozantinib will be administered orally at assigned daily dose levels of 20, 40, or 60 mg. Atezolizumab will be administered at a standard dosing regimen of 1200 mg as an IV infusion once every 3 weeks.

Subjects in the Dose-Escalation Stage on the Standard Dosing Schedule will receive the combination regimen with the first infusion of atezolizumab given on the same day as the first dose of cabozantinib.

In the Combination-Therapy Expansion Cohorts, all initially enrolled subjects and any additional subjects enrolled per Extended Enrollment Option 1 will receive cabozantinib 40 mg in combination with the standard dose of atezolizumab 1200 mg. Additional subjects enrolled per Extended Enrollment Option 2 will receive cabozantinib 60 mg in combination with the standard dose of atezolizumab 1200 mg. For details on the Extended Enrollment Options, see Section 3.5.2.1.

Subjects in the Exploratory SAC Cohorts will receive cabozantinib 60 mg qd.

Subjects in the Exploratory SAA Cohort will receive a standard dosing regimen of atezolizumab (1200 mg IV, q3w).

Subjects who take part in the Second Agent Add-On Stage after exhibiting Investigator-assessed radiographic progression per RECIST 1.1 will receive study treatment as follows:

- Subjects moving to combination therapy from the SAC cohorts who were still receiving 60 mg cabozantinib qd doses will reduce to 40 mg cabozantinib qd doses in the Second Agent Add-On Stage; subjects who were receiving cabozantinib doses of 40 mg qd, 20 mg qd, or 20 mg qod will continue to receive cabozantinib at their current dose level. All these subjects will initiate atezolizumab treatment at 1200 mg IV, q3w.

- Subjects moving to combination therapy from the SAA cohort will continue to receive atezolizumab according to the standard regimen (1200 mg IV, q3w) and will initiate cabozantinib treatment at 40 mg orally, qd.

Further instructions for treatment administration are provided in Sections 6.2.1 and 6.2.2. Special accommodations during the global COVID-19 pandemic are described in Appendix M.

Subjects will receive study treatment as long as they continue to experience clinical benefit as assessed by the investigator or until unacceptable toxicity, the need for subsequent systemic anticancer treatment, or until any other reasons for treatment discontinuation listed in the protocol (Section 3.8). For subjects in combination treatment cohorts, discontinuation of one component of the combination study treatment while continuing to receive the other is allowed but requires Sponsor notification.

For guidance on dose modifications, interruptions, delays, or discontinuations due to AEs, refer to Section 6.5.1.

### 6.2.1 Administration at the Clinic

Cabozantinib:

The first doses of cabozantinib and atezolizumab will be administered at the clinic; for subjects receiving combination treatment, atezolizumab is to be administered first.

The subject will be fasted (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 to monitor for potential AEs. For cabozantinib dosing on subsequent dosing days refer to Section 6.2.2.

Atezolizumab:

Doses of atezolizumab will always be administered intravenously at the clinic by infusion on Day 1 of each 21-day cycle (-2 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 IRRs and with access to emergency services. The initial intravenous (IV) infusion of atezolizumab will be given over 60 min (± 15 min) without premedication for potential IRRs or CRS. Subsequent IV infusions may be given over 30 min (± 10 min) if the initial infusion is tolerated. Premedication for infusion-reaction 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.<br>• Vital signs (blood pressure, pulse, respiratory rate, and temperature) should be recorded within 60 min prior to the infusion.<br>• Atezolizumab should be infused over 60 (± 15) min.<br>• 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.<br>• 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 infusion-related reaction or cytokine-release syndrome with any previous infusion, premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator.<br>• Vital signs should be recorded within 60 min prior to the infusion.<br>• Atezolizumab should be infused over 30 (± 10) min if the previous infusion was tolerated without an infusion-related reaction or cytokine-release syndrome, or 60 (± 15) min if the subject experienced an infusion-related reaction or cytokine release syndrome with the previous infusion.<br>• If the subject experienced an infusion-related reaction or cytokine release syndrome with the previous infusion or if clinically indicated, vital signs should be recorded during the infusion and at 30 (± 5) min after the infusion. |

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 and CRS refer to Appendix I.

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

### 6.2.2 Cabozantinib Administration outside the Clinic

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

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

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

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.

Subjects enrolled in the Dose-Escalation Stage will be expected to complete a cabozantinib-administration diary during the DLT Evaluation Period (Section 5.6.10).

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

## 6.3 Compliance

Subject compliance with outpatient study treatment will be assessed by the site using drug dispensing and return records, progress notes about dose reductions/interruptions, subject interview, and the subject daily diary (DLT Evaluation Period of the Dose-Escalation Stage cohorts only, Section 5.6.10). These data will not be directly recorded in the CRF; rather, the CRF will capture intervals of constant dose and reasons for changes in dose level (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).

## 6.4 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. 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.

## 6.5 Safety Considerations

### 6.5.1 Management of AEs with Dose Reductions and/or Dose Interruptions

Subjects will be monitored for AEs from the time of signing informed consent through 30 days (90 days for AESIs) after the date of the decision to permanently discontinue all study treatment. Subjects will be instructed to notify their physician immediately for any occurring AE. Causality assessment of AEs should include at minimum confounding factors such as disease and

concomitant medications. Adverse event severity will be graded by the investigator according to CTCAE v.4.0.

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

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

    - Examples of VEGFR TKI associated AEs caused by cabozantinib are hypertension and hand-foot syndrome.

    - Examples of irAEs caused by atezolizumab are pneumonitis and endocrinopathies.

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

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

- Study treatment may be continued for mild AEs if appropriate supportive care has been initiated to ameliorate symptoms. Should this be ineffective and toxicities become unacceptable, dose modifications of study treatment should be considered to prevent worsening of toxicity. Moderate to severe AEs usually require dose modifications including dose reductions and/or interruptions.

- Dose interruptions of cabozantinib or atezolizumab for AEs may occur at any time and independently at the discretion of the investigator. If either or both study treatments are interrupted for more than 12 weeks, the sponsor should be contacted to discuss potential treatment continuation.

<u>Cabozantinib:</u>

- The assigned dose for cabozantinib in Cohort 1 of the Dose-Escalation Stage was 40 mg qd. Following review of safety data of the Dose-Escalation Stage by the Cohort Review

Committee, the assigned dose for the Combination-Therapy Expansion Cohorts in the Expansion Stage was determined as 40 mg. The maximum protocol-allowed dose for cabozantinib is 60 mg qd.

- Three dose reduction levels of cabozantinib (40 mg daily, 20 mg daily, and 20 mg qod) are permitted (see Table 6-3).
- For subjects in the Dose-Escalation Stage, dose reductions or interruptions of cabozantinib during the DLT Evaluation Period may result in DLTs (refer to Section 3.5.1.2).
- Dose modification criteria for treatment-related AEs of cabozantinib are shown in Table 6-4.
- Dose reinstitution and re-escalation of cabozantinib after dose interruptions and/or reductions:
    - If the subject recovers from his or her toxicities to CTCAE v.4.0 ≤ Grade 1 or to the baseline value (or lower) and the AE was unrelated to cabozantinib, then cabozantinib may be restarted with no change in dose.
    - If the subject recovers from his or her toxicities to ≤ Grade 1 or to the baseline value (or lower) the AE was deemed possibly related to cabozantinib, then cabozantinib may be restarted at a reduced dose (see Table 6-3). Subjects who initiated treatment with cabozantinib at 40 mg and experience a possibly related AE of Grade 1 or 2 severity may be restarted with no dose change after recovery of the toxicities to ≤ Grade 1 or to the baseline value (or lower) if appropriate supportive care can prevent or minimize the risk of the AE.
    - Subjects receiving a dose of 20 mg qod may be restarted at the same dose if deemed safe at the discretion of the investigator. Subjects unable to tolerate a dose of 20 mg qod should discontinue cabozantinib.
    - For subjects in the Combination-Therapy Expansion Cohorts or the Exploratory SAC Cohorts in the Expansion Stage, and subjects receiving treatment in the Second Agent Add-On Stage, re-escalation of cabozantinib to the previous dose after a dose reduction may be allowed at the discretion of the investigator for AEs which have resolved or recovered to Grade 1 (or baseline value) and are deemed tolerable and easily managed by optimized supportive treatment. A minimum two-week interval is needed between resuming with study treatment and the escalation to the next higher dose level. Dose

re-escalation is not allowed during the Dose-Escalation Stage or following a cabozantinib-related dose reduction for Grade 4 AEs affecting major organs (eg, CNS, cardiac, hepatic, renal). Since the primary objective of the Dose-Escalation stage has been met, the remaining active subjects enrolled in the Dose-Escalation Stage will be allowed to re-escalate cabozantinib to the previous dose level after a dose reduction per the above-mentioned protocol guidelines.

- Intra-subject dose escalation of cabozantinib:
  - During the Expansion Stage and the Second Agent Add-On Stage, escalation of cabozantinib from 40 mg qd to 60 mg qd is allowed after Sponsor approval for subjects who are tolerating the 40 mg cabozantinib dose level well and have been treated on this dose level for at least 4 weeks. In general, subjects who develop clinically relevant AEs (eg, Grade 3 or 4 AEs) are not allowed to escalate cabozantinib from 40 mg qd to 60 mg qd.
  - For the remaining active subjects enrolled in the Dose-Escalation Stage at 40 mg of cabozantinib, escalation of cabozantinib to 60 mg is allowed per the above-mentioned protocol guidelines.
- 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 6.5.2.1.

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

| Assigned Starting Dose | First Dose Level Reduction | Second Dose Level Reduction | Third Dose Level Reduction |
|---|---|---|---|
| 60 mg daily (qd) | 40 mg daily (qd) | 20 mg daily (qd) | 20 mg every other day (qod) |
| 40 mg daily (qd) | 20 mg daily (qd) | 20 mg every other day (qod) | No dose reduction permitted |
| 20 mg daily (qd) | 20 mg every other day (qod) | No dose reduction permitted | — |

Though a dose level of 20 mg every other day (qod) is permitted resulting from dose reductions, that dose level will not be evaluated as an assigned starting dose in either stage of this study. Cabozantinib will be discontinued if a dose of 20-mg cabozantinib every other day (minimum dose) is not tolerated.

**Table 6-4: Dose Modifications for Cabozantinib-Associated AEs**

| CTCAE v.4.0 Grade | Recommended Guidelines for Management[a] |
|---|---|
| Grade 1 AEs | Add supportive care as indicated. Continue cabozantinib at the current dose level if AE is manageable and tolerable. |
| Grade 2 AEs which are tolerable and are easily managed | Continue cabozantinib at the current dose level with supportive care. |
| Grade 2 AEs which are **intolerable** and **cannot be adequately managed** | Cabozantinib should be dose reduced or interrupted.<br>Note: It is recommended that dose interruptions be as brief as possible. |
| Grade 3 AEs (except clinically non-relevant laboratory abnormalities) | Cabozantinib should be interrupted unless the toxicity can be easily managed with a dose reduction of cabozantinib and optimal medical care.<br>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.<br>In general, cabozantinib should be discontinued unless the following criteria are met:<br>• Subject is deriving clear clinical benefit as determined by the investigator and agreed by the Sponsor<br>• Toxicity can be managed with a dose reduction of cabozantinib following recovery to Grade 1 (or baseline) and optimal medical care<br>Sponsor must be contacted to discuss treatment continuation upon resolution of adverse events. |

AE, adverse event.

Note: Cabozantinib dose modification criteria for specific medical conditions are provided in Section 6.5.2.1.

[a] Study treatment dose adjustment is only needed if the toxicity was deemed related to treatment or had an unclear relationship to study treatment.

Atezolizumab:

- The assigned dose for atezolizumab is 1200 mg IV every 3 weeks. Infusion will occur every three weeks (-2 days) on Day 1 of each Cycle.
- Dose interruptions are allowed for atezolizumab (see Table 6-5) but dose reductions are not allowed.
- Dose modification criteria for irAEs and for guidance on reinstituting atezolizumab are shown in Table 6-6.
- 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 and irAEs of atezolizumab (ie, pneumonitis, hepatitis, diarrhea/colitis, myocarditis, endocrinopathies including hypophysitis, and infection) are provided in Section 6.5.2.2.

**Table 6-5: Dose Interruptions of Atezolizumab**

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

q3w, every 3 weeks; irAE, immune-related adverse events

**Table 6-6: Dose Modifications for Atezolizumab-Associated AEs**

| CTCAE v.4.0 Grade | Recommended Management |
|---|---|
| Grade 2 myocarditis<br>Grade 2 pneumonitis<br>Grade 2 nephritis<br>Hepatic events:<br>**Non-HCC Cohorts:**<br>• Asymptomatic with ALT/AST to > 3.0 to ≤ 5.0 x ULN for > 5 days duration, **or**<br>• ALT/AST increases to > 3 to ≤ 5 x ULN with the appearance of worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia, **or**<br>• Total bilirubin increases to > 1.5 to ≤ 3.0 x ULN for > 5 days duration | |
| **HCC Cohort:**<br>• If AST/ALT is within normal limits at baseline and increases to > 3 × ULN to ≤ 10 × ULN, **or**<br>• If AST/ALT is > ULN to ≤ 3 × ULN at baseline and increases to > 5 × ULN to ≤ 10 × ULN, **or**<br>• If AST/ALT is > 3 × ULN to ≤ 5 × ULN at baseline and increases to > 8 × ULN to ≤ 10 × ULN | Delay treatment with atezolizumab<br>Treatment may be resumed in subjects following recovery to Grade 0-1.<br>*(Note: The guidance above applies to all events listed on the left column)* |
| Grade 2 or 3 diarrhea or colitis<br>Grade 2 or 3 myositis<br>Symptomatic adrenal insufficiency, hypothyroidism, or hyperthyroidism; Grade 2 or 3 hypophysitis; or Grade 3 or 4 hyperglycemia<br>Grade 2 ocular inflammatory toxicity<br>Grade 2 or 3 pancreatitis or increases in amylase and/or lipase levels to > 2.0 - 5.0 x ULN with signs or symptoms or to > 5.0 x ULN<br>Grade 3 or 4 infection<br>Grade 2 infusion-related reactions or cytokine release syndrome<br>Grade 3 rash<br>Other Grade 2 or 3 atezolizumab-associated AEs | |

| CTCAE v.4.0 Grade | Recommended Management |
|---|---|
| Grade 3 or 4 myocarditis and/or Grade 2 myocarditis unresolved while withholding atezolizumab<br><br>Grade 4 myositis and/or recurrent Grade 3 myositis<br><br>Grade 3 or 4 pneumonitis<br><br>Grade 3 or 4 nephritis<br><br>Hepatic events:<br><br>**Non-HCC Cohorts:**<br><br>• Symptomatic AST/ALT increases to > 5.0 x ULN, **or**<br>• Asymptomatic AST/ALT increases to > 5 x ULN for > 2 weeks, **or**<br>• AST/ALT increases to > 20.0 x ULN, **or**<br>• Total bilirubin increase to > 3.0 x ULN, **or**<br>• The following hepatic events that do not resolve to Grade 1 or better within 12 weeks<br>o Asymptomatic with ALT/AST to > 3.0 to ≤ 5.0 x ULN, **or**<br>o ALT/AST increases to > 3 to ≤ 5 x ULN with the appearance of worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia, **or**<br>o Total bilirubin increases to > 1.5 to ≤ 3.0 x ULN.<br><br>**HCC Cohort:**<br><br>AST or ALT > 10 × ULN or total bilirubin > 3 × ULN<br><br>Grade 4 diarrhea or colitis<br><br>Grade 4 hypophysitis and/or recurrent hypophysitis<br><br>Myasthenic syndrome/myasthenia gravis, Guillain-Barré or meningoencephalitis (all grades)<br><br>Grade 3 or 4 ocular inflammatory toxicity<br><br>Grade 4 or any grade of recurrent pancreatitis<br><br>Grade 3 or 4 infusion-related reactions or cytokine release syndrome<br><br>Grade 4 rash<br><br>Grade 4 pancreatitis<br><br>Other Grade 4 or recurrent Grade 3 atezolizumab-associated AEs | Permanently discontinue atezolizumab<br><br>*(Note: This guidance applies to all events listed on the left column)* |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; irAE, immune-related adverse event; ULN, upper limit of normal.

Note: Additional information for atezolizumab dose modification criteria and treatment recommendations for irAEs and infusion reactions are provided in Section 6.5.2.2.

### 6.5.2 Warnings, Precautions, Guidelines for Management of Adverse Events

Subjects will be monitored for AEs from the time of signing informed consent through 30 days (90 days for AESIs) after the date of the decision to permanently discontinue treatment. Subjects will be instructed to notify their physician immediately for any occurring AE. Causality assessment of AEs should include at minimum confounding factors such as disease and concomitant medications. Adverse event severity will be graded by the investigator according to CTCAE v.4.0

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

#### 6.5.2.1 Cabozantinib

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

Other medically important but less frequent AEs including arterial thrombotic AEs (eg, TIA, and MI) and venous thrombotic AEs (eg, 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 RPLS.

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

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

Cabozantinib should be discontinued for the following AEs: visceral perforation or fistula formation, severe hemorrhage, serious arterial thromboembolic events, nephrotic syndrome, hypertensive emergency, persistent uncontrolled hypertension despite optimal medical management, and RPLS.

#### 6.5.2.1.1 Gastrointestinal Disorders

Gastrointestinal perforation, GI fistula, and intra-abdominal and pelvic abscess: After starting treatment with cabozantinib, subjects should be monitored for early signs of GI perforation such as abdominal pain, nausea, emesis, constipation, and fever especially if known risk factors for developing GI perforation or fistula (Turnage and Badgwell 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 6-7. 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 6-7: Management of Diarrhea Associated with Cabozantinib**

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

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

#### 6.5.2.1.2 Non-Gastrointestinal Fistula

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

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

#### 6.5.2.1.3 Hemorrhage

Hemorrhagic events, including serious and sometimes fatal events, have been reported with cabozantinib. Subjects should be monitored for bleeding events with serial complete blood 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).

#### 6.5.2.1.4 Thromboembolic events

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

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

#### 6.5.2.1.5 Hypertension

Table 6-8 provides treatment guidelines for hypertension deemed related to cabozantinib. Blood pressure should be monitored in a constant position visit to visit, either sitting or supine in a relaxed setting. Decisions to reduce or interrupt the dose of study treatment must be based on BP readings taken by a medical professional and must be confirmed with a second measurement at least 5 minutes following the first measurement.

Cabozantinib should be discontinued in subjects with hypertensive emergency.

**Table 6-8: Management of Hypertension Associated with Cabozantinib**

| Criteria for Dose Modifications | Treatment/Cabozantinib Dose Modification |
|---|---|
| **Subjects NOT receiving optimized anti-hypertensive therapy** | |
| > 150 mm Hg (systolic)[a] and < 160 mm Hg<br>OR<br>> 100 mm Hg (diastolic) and < 110 mm Hg | • Optimize antihypertensive medications by adding new or additional antihypertensive medications and/or increase dose of existing medications.<br>• Reduce cabozantinib treatment by one dose level if optimal antihypertensive therapy (usually to include 3 agents) does not result in BP < 150 mm Hg systolic and < 100 mm Hg diastolic<br>• If subject is symptomatic interrupt cabozantinib treatment |
| ≥ 160 mm Hg (systolic)<br>OR<br>≥ 110 mm Hg (diastolic) | • Reduce cabozantinib by one dose level[b] or interrupt cabozantinib treatment per investigator discretion<br>• Add new or additional anti-hypertensive medications and/or increase dose of existing medications and monitor subject closely for hypotension. If optimized antihypertensive therapy (usually to include 3 agents) does not result in BP < 150 mm Hg systolic and < 100 mm Hg diastolic, cabozantinib treatment should be dose reduced further or interrupted<br>• Cabozantinib treatment should be dose interrupted if upper limits of systolic BP (≥ 160 mm Hg) are sustained and not adequately manageable or if systolic BP is > 180 mm Hg or sustained diastolic BP > 110 mm Hg, or if subject is symptomatic<br>• Re-start cabozantinib treatment at the most tolerable dose and re-escalate only if BP falls to and is sustained at < 150 mm Hg systolic and < 100 mm Hg diastolic |
| Hypertensive emergency[c] | • Discontinue cabozantinib treatment |

BP, blood pressure; MI, myocardial infarction.

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

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

[c] Hypertensive emergency is defined as uncontrolled elevated BP with clinical evidence of progressive or impending end-organ damage (eg, MI/ischemia, intracranial hemorrhage, cerebral ischemia, pulmonary edema, encephalopathy, kidney damage).

#### 6.5.2.1.6 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.

#### 6.5.2.1.7 Skin and Subcutaneous Tissue Disorders

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

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

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 6-9.

**Table 6-9: Management of Palmar-plantar Erythrodysesthesia (PPE) Associated with Cabozantinib**

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

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

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

#### 6.5.2.1.8 Osteonecrosis

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

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

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

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

#### 6.5.2.1.9 Proteinuria

Proteinuria has been reported with cabozantinib. Proteinuria should be monitored by measuring UPCR. Table 6-10 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 6-10: Management of Proteinuria Associated with Cabozantinib**

| Severity of Proteinuria (UPCR) | Management of Proteinuria |
|---|---|
| Non-UC:<br>≤ 1 mg/mg<br>(≤ 113.1 mg/mmol)<br>**For UC**:<br>≤ 2 mg/mg<br>(≤ 226.2 mg/mmol) | • No change in cabozantinib treatment or monitoring |
| Non-UC:<br>> 1 and < 3.5 mg/mg<br>(> 113.1 and < 395.9 mg/mmol)<br>**For UC**:<br>(> 2 and < 3.5 mg/mg<br>(> 226.2 and < 395.9 mg/mmol) | • Consider confirming with a 24-h protein assessment within 7 days<br>• No change in cabozantinib treatment required if UPCR ≤ 2 mg/mg or urine protein ≤ 2 g/24 h on 24-h urine collection.<br>• 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.<br>• 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.) |
| All Tumor Types:<br>≥ 3.5 mg/mg<br>(≥ 395.9 mg/mmol) | • Interrupt cabozantinib treatment pending repeat UPCR monitoring within 7 days and/or 24-h urine protein.<br>• If ≥ 3.5 mg/mg on repeat UPCR monitoring, continue to interrupt cabozantinib treatment and check UPCR every 7 days. If UPCR decreases to < 2 mg/mg, restart cabozantinib treatment at a reduced dose and monitoring of UPCR until it remains < 2 mg/mg on two consecutive measurements. If UPCR monitoring is determined to be stable (< 20% change) for 1 month then continue with UPCR monitoring per protocol or as clinically indicated. |
| Nephrotic syndrome | • Discontinue cabozantinib treatment |

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

#### 6.5.2.1.10 Nervous System Disorders

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

RPLS 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.

#### 6.5.2.1.11 Infections and Infestations

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

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

#### 6.5.2.1.12 Blood and Lymphatic System Disorders

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

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

#### 6.5.2.1.13 Fatigue

Common causes of fatigue, such as anemia, deconditioning, emotional distress (depression and/or anxiety), poor nutrition, dehydration, sleep disturbance, and hypothyroidism should be

ruled out and treated according to standard of care. Pharmacological management should be considered after disease specific morbidities have been excluded when not prohibited.

#### 6.5.2.1.14 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.

#### 6.5.2.1.15 Corrected QT Prolongation

The effect of orally administered cabozantinib 140 mg qd on QTc interval was evaluated in a placebo-controlled study in subjects with 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 > 500 ms, 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, 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)
- Repeat ECG triplicates hourly until the average QTcF is ≤ 500 msec, or otherwise determined by consultation with a cardiologist or appropriate expert.
- Send copies of ECGs to central ECG laboratory for independent read

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

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

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

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

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

#### 6.5.2.1.16 Electrolyte Disorders

Serum electrolyte disorders including hyponatremia, hypokalemia, hypomagnesemia, and hypophosphatemia have been reported during treatment with cabozantinib, and serum electrolyte levels should be monitored frequently while receiving cabozantinib. Clinically relevant

electrolyte disorders should be managed according to the dose modification guidelines as outlined in Table 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.

#### 6.5.2.1.17 Endocrine Disorders

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

#### 6.5.2.1.18 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, infection) should be evaluated.

Management guidelines for hepatotoxicity related to cabozantinib treatment for subjects in **non-HCC** cohorts are provided in Table 6-11.

**Table 6-11: Management of Hepatotoxicity Associated with Cabozantinib for Subjects in Non-HCC Cohorts**

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

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; DILI, drug-induced liver injury.
Note: The guidance for dose modifications for bilirubin abnormalities applies only to subjects without Gilbert's Disease.

Guidelines for management of hepatotoxicity related to cabozantinib treatment for subjects in the HCC cohort is provided in Table 6-12. Since the HCC cohort allows subjects with ALT/AST up to 5 x ULN at study entry, hepatotoxicity AEs are expected to occur relatively frequently due to their disease. These guidelines are to be followed for cabozantinib-associated liver function abnormalities in these subjects.

**Table 6-12 Management of Hepatotoxicity Associated with Cabozantinib for Subjects in the HCC Cohort**

| Severity of Event (Transaminase [ALT or AST] and total bilirubin Elevations) | Management |
|---|---|
| If ALT or AST is ≤ 3.0 × ULN at baseline and increases to ≥ 5.0 × ULN (total bilirubin ≤ 2.0 x ULN) | • Interrupt cabozantinib<br>• Monitor LFTs more frequently until return to baseline values<br>• If event resolves to baseline, or values stabilize at clinically acceptable levels, cabozantinib may be resumed at a reduced dose |
| If ALT or AST is > 3.0 × ULN to ≤ 5.0 × ULN at baseline and doubles compared with the baseline values (total bilirubin ≤ 2.0 x ULN)<br>**OR**<br>If ALT or AST is > 3.0 × ULN to ≤ 5.0 × ULN at baseline and increases are less than double but are accompanied by progressive elevations of total bilirubin and/or elevations of coagulation tests (eg, INR) (total bilirubin ≤ 2.0 x ULN) | • Interrupt cabozantinib<br>• Monitor LFTs more frequently until return to baseline values.<br>• If event resolves to baseline, or values stabilize at clinically acceptable levels, cabozantinib may be resumed at a reduced dose |
| Drug-related ALT or AST > 10 × ULN for > 2 weeks<br>OR<br>Drug-related ALT or AST > 15 × ULN irrespective of duration | • Discontinue cabozantinib unless these laboratory abnormalities have recovered to Grade 1 or baseline level after an interruption and the Sponsor has approved reinstitution of cabozantinib |
| If hepatic dysfunction is not reversible despite temporary interruption of cabozantinib or drug-related ALT or AST > 3 × ULN in combination with total bilirubin > 2 × ULN without reasonable other explanation, consistent with DILI | • Discontinue cabozantinib |

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

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

#### 6.5.2.2 Atezolizumab

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

Subjects treated with atezolizumab may also develop IRRs and CRS as well as irAEs such as myocarditis, pneumonitis, hepatitis, colitis, nephritis, endocrinopathies (hypophysitis, thyroid disorders, adrenal insufficiency, Type 1 diabetes), skin disorders, ocular events, neurological toxicity (myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome or meningoencephalitis), pancreatitis, myositis, and embryo-fetal toxicity. Management guidance for atezolizumab-associated AEs is provided in Sections 6.5.2.2.1 to 6.5.2.2.16.

*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.*

##### 6.5.2.2.1 Infusion-Related Reactions and Cytokine-Release Syndrome

Infusion-related reactions (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.

Cytokine-release syndrome (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 administration of Cycle 1 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. Therefore, consolidated guidelines for medical management and CTCAE grading of IRRs and CRS are provided in Appendix I.

#### 6.5.2.2.2 Immune-Related Pulmonary Events

Dyspnea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of atezolizumab. 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, PE, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. Management guidelines for pulmonary events are provided in Table 6-13.

**Table 6-13: Management Guidelines for Immune-Related Pulmonary Events, Including Pneumonitis**

| Severity of Event | Management |
|---|---|
| Grade 1 | • Continue atezolizumab and monitor closely<br>• Re-evaluate on serial imaging<br>• Consider subject referral to pulmonary specialist<br>• For recurrent pneumonitis, treat as a Grade 3 or 4 event |
| Grade 2 | • Withhold atezolizumab<br>• Refer subject to pulmonary and infectious disease specialists and consider bronchoscopy or BAL<br>• Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent.<br>• Resume atezolizumab if event resolves to Grade 1 or better within 12 weeks[a,b]<br>• Permanently discontinue atezolizumab and contact the Sponsor if event does not resolve to Grade 1 or better within 12 weeks[a,b,c]<br>• For recurrent events, treat as a Grade 3 or 4 event |
| Grade 3 or 4 | • Permanently discontinue atezolizumab and contact the Sponsor[c]<br>• Bronchoscopy or BAL is recommended.<br>• Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent.<br>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent<br>• If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month |

BAL, bronchoscopic alveolar lavage.

[a] 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.

[b] 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 agreed upon by the investigator and the Sponsor.

[c] Resumption of atezolizumab may be considered in subjects who are deriving benefit and have fully recovered from the immune-related event. Subjects can be rechallenged with atezolizumab only after approval has been documented by both the Investigator (or an appropriate delegate) and the Sponsor.

#### 6.5.2.2.3 Immune-Related Colitis or Diarrhea

Immune-related colitis has been associated with the administration of atezolizumab. Management guidelines for diarrhea or colitis are provided in Table 6-14.

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 6-14: Management Guidelines for Immune-Related Diarrhea or Colitis**

| Severity of Event | Management |
|---|---|
| Grade 1 | • Continue atezolizumab<br>• Initiate symptomatic treatment<br>• Endoscopy is recommended if symptoms persist for > 7 days<br>• Monitor closely |
| Grade 2 | • Withhold atezolizumab<br>• Initiate symptomatic treatment<br>• Subject referral to GI specialist is recommended<br>• For recurrent events or events that persist > 5 days, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent<br>• Resume atezolizumab if event resolves to Grade 1 or better within 12 weeks[a,b]<br>• Permanently discontinue atezolizumab and contact the Sponsor if event does not resolve to Grade 1 or better within 12 weeks[a,b,c] |
| Grade 3 | • Withhold atezolizumab<br>• Refer subject to GI specialist for evaluation and confirmatory biopsy<br>• 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<br>• Resume atezolizumab if event resolves to Grade 1 or better within 12 weeks[a,b]<br>• Permanently discontinue atezolizumab and contact the Sponsor if event does not resolve to Grade 1 or better within 12 weeks[a,b,c] |
| Grade 4 | • Permanently discontinue atezolizumab and contact the Sponsor[c]<br>• Refer subject to GI specialist for evaluation and confirmation biopsy.<br>• 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.<br>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.<br>• If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month. |

GI, gastrointestinal; IV, intravenous

[a] 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.

[b] 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 agreed upon by the investigator and the Sponsor.

[c] Resumption of atezolizumab may be considered in subjects who are deriving benefit and have fully recovered from the immune-related event. Subjects can be rechallenged with atezolizumab only after approval has been documented by both the Investigator (or an appropriate delegate) and the Sponsor.

#### 6.5.2.2.4 Immune-related Endocrinopathies

Thyroid disorders, adrenal insufficiency, and hypophysitis have been associated with the administration of atezolizumab. Management guidelines for endocrine events are provided in Table 6-15.

Monitor for signs and symptoms of hypophysitis. Subjects with unexplained symptoms such as 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. TSH, prolactin, and a morning cortisol level will help to differentiate primary adrenal insufficiency from primary pituitary insufficiency.

**Table 6-15: Management Guidelines for Endocrine Events**

| Event | Management |
|---|---|
| Hypophysitis (pan-hypopituitarism) Grade 2-3 | • Withhold atezolizumab for up to 12 weeks after event onset[a]<br>• Refer patient to endocrinologist.<br>• Perform brain MRI (pituitary protocol).<br>• 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.<br>• Initiate hormone replacement therapy if clinically indicated.<br>• If event resolves to Grade 1 or better, resume atezolizumab.[a]<br>• If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Sponsor.[b]<br>• For recurrent hypophysitis, treat as a Grade 4 event. |
| Hypophysitis (pan-hypopituitarism) Grade 4 | • Permanently discontinue atezolizumab and contact the Sponsor.<br>• Refer patient to endocrinologist.<br>• Perform brain MRI (pituitary protocol).<br>• 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.[c]<br>• Initiate hormone replacement therapy if clinically indicated. |
| Asymptomatic hypothyroidism | • Continue atezolizumab<br>• Initiate treatment with thyroid replacement hormone<br>• Monitor TSH every 3 weeks with a close monitoring for any sign and symptom |
| Symptomatic hypothyroidism | • Withhold atezolizumab<br>• Initiate treatment with thyroid replacement hormone<br>• Monitor TSH weekly<br>• Consider subject referral to endocrinologist.<br>• Resume atezolizumab when symptoms are controlled and thyroid function is improving |
| Asymptomatic hyperthyroidism | **TSH ≥ 0.1 mU/L and < 0.5 mU/L**:<br>• Continue atezolizumab<br>• Monitor TSH every 4 weeks<br>**TSH < 0.1 mU/L**:<br>• Follow guidelines for symptomatic hyperthyroidism |

| Event | Management |
|---|---|
| Symptomatic hyperthyroidism | • Withhold atezolizumab<br>• Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed<br>• Consider subject referral to endocrinologist<br>• Resume atezolizumab when symptoms are controlled and thyroid function is improving<br>• Permanently discontinue atezolizumab and contact the Sponsor for life-threatening immune-related hyperthyroidism[b] |
| Symptomatic adrenal insufficiency Grade 2–4 | • Withhold atezolizumab[c]<br>• Refer subject to endocrinologist<br>• Perform appropriate imaging<br>• 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.<br>• Resume atezolizumab if event resolves to Grade 1 or better and subject is stable on replacement therapy (if required) within 12 weeks[a,c]<br>• 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 within 12 weeks[a,b,c] |
| Hyperglycemia Grade 1 or 2 | • Continue atezolizumab<br>• Initiate treatment with insulin if needed<br>• Monitor for glucose control |
| Hyperglycemia Grade 3 or 4 | • Withhold atezolizumab.<br>• Initiate treatment with insulin.<br>• Monitor for glucose control.<br>• Resume atezolizumab when symptoms resolve and glucose levels are stable. |

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

[a] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Sponsor.

[b] Resumption of atezolizumab may be considered in subjects who are deriving benefit and have fully recovered from the immune-related event. Subjects can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Sponsor.

[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.

#### 6.5.2.2.5 Immune-Related Dermatologic Events

Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash were mild in severity and self-limited, with or without pruritus. 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 6-16.

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

| Severity of Event | Management of Skin Disorder |
|---|---|
| Grade 1 | • Continue atezolizumab.<br>• Consider treatment with topical corticosteroids and/or other symptomatic therapy (eg, antihistamines). |
| Grade 2 | • Continue atezolizumab.<br>• Consider subject referral to dermatologist.<br>• Initiate treatment with topical corticosteroids.<br>• Consider treatment with higher-potency topical corticosteroids if event does not improve |
| Grade 3 | • Delay atezolizumab.<br>• Refer subject to dermatologist.<br>• 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.<br>• Resume atezolizumab if event resolves to Grade 1 or better within 12 weeks.[a,c]<br>• Permanently discontinue atezolizumab and contact Sponsor if event does not resolve to Grade 1 or better within 12 weeks.[a,b,c] |
| Grade 4 | • Permanently discontinue atezolizumab and contact Sponsor. |

[a] 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.

[b] 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 agreed upon by the investigator and the Sponsor.

[c] Resumption of atezolizumab may be considered in subjects who are deriving benefit and have fully recovered from the immune-related event. Subjects can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Sponsor.

#### 6.5.2.2.6 Immune-Related Ocular Events

Treatment-emergent ocular events have been associated with atezolizumab. Management guidelines for ocular events are provided in Table 6-17.

**Table 6-17: Atezolizumab Management Guidance of Immune-Related Ocular Events**

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

[a] 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.

[b] 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 agreed upon by the investigator and the Sponsor.

[c] Resumption of atezolizumab may be considered in subjects who are deriving benefit and have fully recovered from the immune-related event. Subjects can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or designee) and the Sponsor.

#### 6.5.2.2.7 Immune-Related Meningoencephalitis

Immune-related meningoencephalitis is an identified risk associated with the administration of atezolizumab. Immune-related meningoencephalitis should be suspected in any subject presenting with signs or symptoms suggestive of meningitis or encephalitis, including, but not limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction, 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 6-18.

**Table 6-18: Management Guidelines for Immune-Related Meningoencephalitis**

| Severity of Event | Management |
|---|---|
| All grades | • Permanently discontinue atezolizumab and contact the Sponsor[a]<br>• Refer subject to neurologist<br>• 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<br>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent<br>• If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month |

IV, intravenous.

[a] Resumption of atezolizumab may be considered in subjects who are deriving benefit and have fully recovered from the immune-related event. Subjects can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Sponsor.

#### 6.5.2.2.8 Immune-Related Motor and Sensory Neuropathy

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

**Table 6-19: Management Guidelines for Immune-Related Neurologic Disorders**

| Event | Management |
|---|---|
| Immune-related neuropathy Grade 1 | • Continue atezolizumab<br>• Investigate etiology |
| Immune-related neuropathy Grade 2 | • Withhold atezolizumab<br>• Investigate etiology<br>• Initiate treatment as per institutional guidelines<br>• Resume atezolizumab if event resolves to Grade 1 or better within 12 weeks[a,b]<br>• Permanently discontinue atezolizumab and contact the Sponsor if event does not resolve to Grade 1 or better within 12 weeks[a,b,c] |
| Immune-related neuropathy Grade 3 or 4 | • Permanently discontinue atezolizumab and contact the Sponsor[c]<br>• Initiate treatment as per institutional guidelines. |
| Myasthenia gravis and Guillain-Barré syndrome, any grade | • Permanently discontinue atezolizumab and contact the Sponsor[c]<br>• Refer subject to neurologist.<br>• Initiate treatment as per institutional guidelines.<br>• Consider initiation of 1–2 mg/kg/day oral or IV prednisone or equivalent. |

IV, intravenous.

[a] 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.

[b] 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 agreed upon by the investigator and the Sponsor.

[c] Resumption of atezolizumab may be considered in subjects who are deriving benefit and have fully recovered from the immune-related event. Subjects can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Sponsor.

#### 6.5.2.2.9 Immune-Related Pancreatitis

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

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

| Event | Management |
|---|---|
| Amylase and/or lipase > ULN - 1.5 x ULN | • Continue atezolizumab<br>• Monitor amylase and lipase prior to dosing |
| Amylase and/or lipase > 1.5 - 2.0 x ULN, or > 2.0 - 5.0 x ULN and asymptomatic | • Continue atezolizumab<br>• Monitor amylase and lipase weekly<br>• For prolonged elevation (eg, > 3 weeks), consider treatment with 10 mg/day oral prednisone or equivalent |
| Amylase and/or lipase > 2.0 - 5.0 x ULN with signs or symptoms, or > 5.0 x ULN | • Withhold atezolizumab<br>• Refer subject to GI specialist<br>• Monitor amylase and lipase every other day<br>• If no improvement, consider treatment with 1–2 mg/kg/day oral prednisone or equivalent<br>• Resume atezolizumab if event resolves to Grade 1 or better within 12 weeks[a,b]<br>• Permanently discontinue atezolizumab and contact the Sponsor if event does not resolve to Grade 1 or better within 12 weeks[a,b,c]<br>• For recurrent events, permanently discontinue atezolizumab and contact the Sponsor[c] |
| Immune-related pancreatitis, Grade 2 or 3 | • Withhold atezolizumab<br>• Refer subject to GI specialist<br>• 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<br>• Resume atezolizumab if event resolves to Grade 1 or better within 12 weeks[a,b]<br>• Permanently discontinue atezolizumab and contact the Sponsor if event does not resolve to Grade 1 or better within 12 weeks[a,b,c]<br>• For recurrent events, permanently discontinue atezolizumab and contact the Sponsor[c] |
| Immune-related pancreatitis, Grade 4 | • Permanently discontinue atezolizumab and contact the Sponsor[c]<br>• Refer subject to GI specialist.<br>• 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.<br>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.<br>• If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month. |

GI, gastrointestinal; IV, intravenous.

[a] 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.

[b] 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 agreed upon by the investigator and the Sponsor.

[c] Resumption of atezolizumab may be considered in subjects who are deriving benefit and have fully recovered from the immune-related event. Subjects can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Sponsor.

#### 6.5.2.2.10 Immune-Related Myocarditis

Non-fatal myocarditis has been associated with the administration of atezolizumab. Guidelines for management of immune-related myocarditis are presented in Table 6-21.

**Table 6-21: Management Guidelines for Immune-Related Myocarditis**

| Event | Management |
|---|---|
| Immune-related myocarditis, Grade 1 | • Refer patient to cardiologist<br>• Initiate treatment as per institutional guidelines. |
| Immune-related myocarditis, Grade 2 | • Withhold atezolizumab for up to 12 weeks after event onset and contact Sponsor.<br>• Refer patient to cardiologist<br>• Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate.<br>• Consider treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement.[a]<br>• If event resolves to Grade 1 or better, resume atezolizumab.[b]<br>• If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Sponsor. [c] |
| Immune-related myocarditis, Grade 3-4 | • Permanently discontinue atezolizumab and contact the Sponsor.[c]<br>• Refer patient to cardiologist<br>• Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate.<br>• Initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement.[a,b]<br>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.<br>• If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month. |

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

[a] 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.

[b] 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 agreed upon by the investigator and the Sponsor.

[c] Resumption of atezolizumab may be considered in subjects who are deriving benefit and have fully recovered from the immune-related event. Subjects can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Sponsor.

#### 6.5.2.2.11 Immune-Related Nephritis

Immune-related nephritis is a relatively rare complication of ICI therapy with the most common reported underlying pathology being acute tubulo-interstitial nephritis. The most common presentation is an asymptomatic increase in creatinine levels. In the absence of alternative etiologies (eg, prerenal and postrenal causes, and concomitant medications), immune-related nephritis is defined as renal dysfunction requiring steroid treatment and/or confirmed by biopsy.

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.

Guidelines for management of immune-related nephritis are presented in Table 6-22.

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

| Event | Management |
|---|---|
| Renal event, Grade 1 | • Continue atezolizumab.<br>• Monitor kidney function, including creatinine, closely until values resolve to within normal limits or to baseline values. |
| Renal event, Grade 2 | • Withhold atezolizumab for up to 12 weeks after event onset. [a]<br>• Refer patient to renal specialist.<br>• Initiate treatment with corticosteroids equivalent to 1−2 mg/kg/day oral prednisone.<br>• If event resolves to Grade 1 or better, resume atezolizumab. [b]<br>• 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.<br>• Refer patient to renal specialist and consider renal biopsy.<br>• Initiate treatment with corticosteroids equivalent to 1−2 mg/kg/day oral prednisone.<br>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.<br>• 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 agreed upon by the Investigator and the Sponsor.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Subjects can be re-challenged with atezolizumab only after approval has been documented by both the Investigator (or an appropriate delegate) and the Sponsor.

#### 6.5.2.2.12 Immune-Related Myositis

Immune-related myositis has been associated with the administration of atezolizumab. Dermatomyositis and polymyositis are amongst the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatinine-kinase increase), and imaging (electromyography/MRI) features and is confirmed with a muscle biopsy. Atezolizumab should be withheld for moderate or severe (Grade 2 or 3) immune-related myositis and permanently discontinued for recurrent severe or life-threatening myositis (recurrent Grade 3 or Grade 4). Please refer the subject to rheumatologist and/or neurologist and consider muscle biopsy and supportive measures as clinically indicated. Corticosteroids treatment with 1-2 mg/kg/day IV methylprednisolone or higher-dose bolus if severely compromised (weakness severely limiting mobility, cardiac function, respiratory function, dysphagia) and/or additional immunosuppressive agents should be administered for ≥ Grade 2 events or if the event does not improve after initial corticosteroids.

Detailed guidelines for management of immune-related myositis are presented in Table 6-23.

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

| Event | Management |
|---|---|
| Immune-related myositis, Grade 1 | • Continue atezolizumab<br>• Refer subject to rheumatologist or neurologist<br>• 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.<br>• Refer subject to rheumatologist or neurologist<br>• Initiate treatment as per institutional guidelines<br>• 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.<br>• If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent<br>• If event resolves to Grade 1 or better, resume atezolizumab.[b]<br>• If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Sponsor.[c] |

| Event | Management |
|---|---|
| Immune-related myositis, Grade 3 | • Withhold atezolizumab for up to 12 weeks after event onset[a] and contact the Sponsor<br>• Refer subject to rheumatologist or neurologist<br>• Initiate treatment as per institutional guidelines<br>• Respiratory support may be required in more severe cases<br>• 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.<br>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.<br>• If event resolves to Grade 1 or better, resume atezolizumab.[b]<br>• If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Sponsor.[c]<br>• For recurrent events, treat as a Grade 4 event |
| Immune-related myositis, Grade 4 | • Permanently discontinue atezolizumab and contact the Sponsor.[c]<br>• Refer subject to rheumatologist or neurologist<br>• Initiate treatment as per institutional guidelines. Respiratory support may be required in more severe cases<br>• 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.<br>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.<br>• 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 agreed upon by the investigator and the Sponsor.

[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. Subjects can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Sponsor.

#### 6.5.2.2.13 Hemophagocytic Lymphohistiocytosis and Macrophage Activation Syndrome

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

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 < $100 \times 10^9$/L (100,000/μL)
  - ANC < $1.0 \times 10^9$/L (1000/μL)
- Fasting triglycerides > 2.992 mmol/L (265 mg/dL) and/or fibrinogen < 1.5 g/L (150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell activity
- Ferritin > 500 mg/L (500 ng/mL)
- Soluble 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 patient should be classified as having MAS if the following criteria are met:

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

Patients with suspected HLH or MAS should be treated according to the guidelines in Table 6-24.

**Table 6-24: Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome**

| Event | Management |
|---|---|
| Suspected HLH or MAS | • Permanently discontinue atezolizumab and contact Medical Monitor.<br>• Consider patient referral to hematologist.<br>• Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines.<br>• Consider initiation of IV corticosteroids and/or an immunosuppressive agent.<br>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.<br>• If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month. |

HLH, hemophagocytic lymphohistiocytosis; MAS, macrophage activation syndrome

#### 6.5.2.2.14 Other Immune-Related Adverse Events

For management of other irAEs not included in Sections 6.5.2.2.1 through 6.5.2.2.16, 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

#### 6.5.2.2.15 Embryo-Fetal Toxicity

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

#### 6.5.2.2.16 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 in all tumor types except HCC are provided in Table 6-25; management guidelines for hepatic events in HCC subjects (who may enter the study with elevations of AST/ALT up to 5 × ULN at baseline) are provided in Table 6-26.

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

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

**Table 6-25: Management Guidelines for Hepatic Events (All Tumor Types Except HCC)**

| Severity of Event | Management |
|---|---|
| If AST or ALT is within normal limits at baseline and increases to<br>> ULN - 3.0 x ULN<br>OR<br>Total bilirubin increases to<br>> ULN - 1.5 x ULN | • Continue atezolizumab<br>• Monitor LFTs until values resolve to within normal limits |
| If asymptomatic with elevation of ALT or AST to > 3.0 - 5.0 x ULN<br>OR<br>Total bilirubin increases to<br>> 1.5 - 3.0 x ULN | **All events:**<br>• Monitor LFTs more frequently until return to baseline values<br>**Events of > 5 days' duration:**<br>• Withhold atezolizumab<br>• Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent<br>• Resume atezolizumab if event resolves to Grade 1 or better within 12 weeks[a,b]<br>• Permanently discontinue atezolizumab and contact the Sponsor if event does not resolve to Grade 1 or better within 12 weeks[a,b,c] |
| ALT or AST increases to > 3 to ≤ 5 x ULN with the appearance of worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia | • Monitor LFTs more frequently until return to baseline values<br>• Withhold atezolizumab<br>• Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent<br>• Resume atezolizumab if event resolves to Grade 1 or better within 12 weeks[a,b]<br>• Permanently discontinue atezolizumab and contact the Sponsor if event does not resolve to Grade 1 or better within 12 weeks[a,b,c] |
| If asymptomatic AST or ALT increases to > 5 x ULN for > 2 weeks<br>OR<br>ALT or AST increases to > 5.0 x ULN with the appearance of worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia<br>OR<br>ALT or AST increases to > 20.0 x ULN<br>OR<br>Total bilirubin increase to<br>> 3.0 x ULN | • Permanently discontinue atezolizumab and contact the Sponsor[c]<br>• Consider subject referral to GI specialist for evaluation and liver biopsy to establish etiology of hepatic injury.<br>• Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent.<br>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.<br>• If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month. |

GI, gastrointestinal; LFT, liver function test.

[a] 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.

[b] 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 agreed upon by the investigator and the Sponsor.

[c] Resumption of atezolizumab may be considered in subjects who are deriving benefit and have fully recovered from the immune-related event. Subjects can be rechallenged with atezolizumab only after approval has been documented by both the Investigator (or an appropriate delegate) and the Sponsor.

**Table 6-26: Management Guidelines for Hepatic Events (HCC Subjects Only)**

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

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

[a] Atezolizumab may be withheld for a 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 agreed upon by the investigator and the Sponsor.

[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. Subjects can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Sponsor.

#### 6.5.2.3 Management Guidelines for Hepatic Encephalopathy

Hepatic encephalopathy is a brain dysfunction caused by liver insufficiency. Hepatic encephalopathy is not uncommon in HCC patients and can be due to acute liver failure, portal systemic shunting and cirrhosis (Wong et al 2011, Willson et al 2013).Guidelines for management of hepatic encephalopathy are presented in Table 6-27.

**Table 6-27: Management of Hepatic Encephalopathy Associated with Study Treatment**

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

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

# 7 CONCOMITANT MEDICATIONS AND THERAPIES

## 7.1 Allowed Therapy

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

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

- Bisphosphonates and/or denosumab can be used to control bone loss or hypercalcemia if the benefit outweighs the risk per the investigator's discretion (Section 6.5.2.1.8).

  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. 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 6.5) 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 specified direct factor Xa inhibitors rivaroxaban, edoxaban, or apixaban is allowed if it can be provided safely and effectively under the following circumstances:

  At the time of first dose of study treatment:

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

  - *Therapeutic doses of LMWH or specified direct factor Xa inhibitors rivaroxaban, edoxaban, or apixaban* are allowed in subjects (excluding HCC subjects) if the subject has no evidence of brain metastasis, has been on a stable dose of the anticoagulant for at least 1 week, and has had no clinically significant hemorrhagic complications from the anticoagulation regimen or the tumor. See Section 7.2 for prohibited anticoagulants.

  - *Subjects with HCC may be treated with therapeutic LMWH but must have a screening platelet count of > 100,000/µL* (no oral anticoagulants are allowed in subjects with HCC).

  After first dose of study treatment:

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

  - *Therapeutic doses of LMWH or specified direct factor Xa oral inhibitors rivaroxaban, edoxaban, or apixaban* are allowed in subjects (excluding HCC subjects) 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 6.5.2.1.4. See Section 7.2 for prohibited anticoagulants.

  - *Subjects with HCC may be treated with therapeutic LMWH* (no oral anticoagulants are allowed in subjects with HCC).

  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 the potential adverse drug reactions, monitoring laboratory parameters,

and 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 anticoagulants and accepted clinical practice guidelines.

Potential drug interactions with cabozantinib are summarized in Section 7.3.1. The drug interaction potential of atezolizumab is unknown. Refer to the local prescribing information and the atezolizumab Investigator's Brochure.

## 7.2 Prohibited or Restricted Therapy

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

- Any investigational agent or investigational medical device.
- Oral anticoagulants with coumarin agents (eg, warfarin), direct thrombin and factor Xa inhibitors (unless otherwise specified in Section 7.1), platelet inhibitors (eg, clopidogrel), and chronic use of aspirin above low dose levels for cardioprotection per local applicable guidelines, until 4 weeks after cabozantinib has been permanently discontinued.
    - No oral anticoagulants are allowed in subjects with HCC.
- Any nonprotocol systemic anticancer treatment (eg, chemotherapy, hormonal therapy, immunotherapy, radionuclides, 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 with mCRPC without bilateral orchiectomy.
- Immunosuppressive agents including immunosuppressive doses of systemic corticosteroids with exceptions as stated in Section 7.1.
- 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) in the Combination-Therapy Expansion Cohorts and exploratory SAA Cohort. The use of inactivated (killed) vaccines for the prevention of infectious disease is allowed.
- Metamizole (dipyrone) because of its potential for causing agranulocytosis.

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

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

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

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

- Chronic co-administration of cabozantinib with strong inducers of the CYP3A4 family (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 for subjects receiving cabozantinib. See Appendix J for further details.

- 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 cabozantinib and should be avoided in subjects receiving cabozantinib. See Appendix J for further details.

Additional information on potential drug interactions with cabozantinib is provided in Section 7.3.1.

*Refer to the local prescribing information and the atezolizumab Investigator's Brochure for drugs to be avoided when taking atezolizumab.*

## 7.3 Potential Drug Interactions

### 7.3.1 Potential Drug Interactions with Cabozantinib

*Cytochrome P450:* Data from a clinical drug interaction study (Study XL184-008) show that clinically relevant steady-state concentrations of cabozantinib appear to have no marked effect on the area under the plasma concentration-vs-time curve (AUC) of co-administered rosiglitazone, a CYP2C8 substrate. Therefore, cabozantinib is not anticipated to markedly inhibit CYP2C8 in the clinic, and by inference, is not anticipated to markedly inhibit other CYP450 isozymes that have lower [I]/Ki values compared with CYP2C8 (ie, CYP2C9, CYP2C19, CYP2D6, CYP1A2, and CYP3A4). In vitro data indicate that cabozantinib is unlikely to induce 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. 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. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme inhibition potential is recommended.

For lists of substrates, inducers, and inhibitors of selected CYP450 isozyme pathways, refer to Appendix J.

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

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

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

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

# 8 SAFETY

## 8.1 Adverse Events and Laboratory Abnormalities

### 8.1.1 Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation subject participating in a clinical study 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, ECG findings, or vital signs), symptom, or disease temporally associated with the use of an investigational product, regardless of whether or not the event is assessed as related to the investigational product. This requirement includes specific events or symptoms associated with cancer progression or general clinical deterioration to ensure potential toxicities are not overlooked. Radiographic progression without associated clinical sequelae is not considered an AE: terms such as “disease progression” should be avoided. Pre-existing medical conditions that worsen during a study will be recorded as AEs. Abnormal laboratory values, ECG findings, or vital signs are to be recorded as SAEs if they meet the criteria described in Section 8.2.

All untoward events that occur after informed consent through 30 days (90 days for AESIs) after the date of the decision to permanently discontinue study treatment are to be recorded in source documents by the investigational site. See the CRF Completion Guidelines for instructions on entering these data on Medical History and/or AE CRFs and Section 8.2 for SAE reporting requirements. The date of the decision to discontinue study treatment is defined for each subject as the later of (a) the date of the decision of the investigator to permanently discontinue study treatment or (b) the date of the last dose of study treatment taken by the subject.

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

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

- **Not Related**: An event is assessed as not related to study treatment if it is attributable to another cause and/or there is no evidence to support a causal relationship.
- **Related**: An event is assessed as related to study treatment when there is a reasonable possibility that study treatment caused the event. Reasonable possibility means there is evidence to suggest a causal relationship between study treatment and the event. This event is

called a suspected adverse reaction. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

### 8.1.2 Laboratory Abnormalities

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

## 8.2 Serious Adverse Events

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

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

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

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

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

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

- All SAEs that occur after informed consent and through 30 days (90 days for AESIs) after the date of the decision to permanently discontinue study treatment (or the date the subject is deemed to be a screen failure).

- Any SAEs assessed as related to study treatment or study procedures, even if the SAE occurs more than 30 days after the date of the decision to permanently discontinue study treatment.

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

SAEs that occur after informed consent through 30 days (90 days for AESIs) after the date of the decision to permanently discontinue of study treatment must also be recorded on the CRF page.

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

In all cases, the investigator should continue to monitor the clinical situation and report all material facts relating to the progression or outcome of the SAE. Furthermore, the investigator may be required to provide supplementary information as requested by the Sponsor's Drug Safety personnel or designee.

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

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

- Death will not be reported as an SAE, but as an outcome of a specific SAE, unless the event preceding the death is unknown. Terms of "Unexplained Death" or "Death from unknown origin" may be used when the cause is unknown. In these circumstances the cause of death must be investigated and the diagnosis amended when the etiology has been identified. If an autopsy was performed, the autopsy report should be provided.

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

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

    - Prespecified study hospitalizations for observation.

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

### 8.2.1 Regulatory Reporting

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

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

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

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

## 8.3 Adverse Events of Special Interest for Atezolizumab

Adverse events of special interest (AESIs) for atezolizumab consist of immune-mediated adverse events associated with ICIs, cases of potential drug-induced liver injury, and suspected transmission of an infectious agent by the study treatment (Table 8-1).

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

Guidance for management of immune-mediated adverse events associated with atezolizumab is provided in the protocol (Section 6.5.2.2) and can also be found in the local prescribing information and atezolizumab Investigator's Brochure.

**Table 8-1: Adverse Events of Special Interest for Atezolizumab**

- Cases of potential DILI that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice as based on the following observations:
    - **For non-HCC subjects (Hy's Law)**:
        - 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
    - **For HCC subjects**:
        - Treatment-emergent ALT or AST > 3 × baseline value in combination with total bilirubin > 2 × ULN (of which ≥ 35% is direct bilirubin)
        - Treatment-emergent ALT or AST > 3 × baseline value in combination with clinical jaundice
- Suspected transmission of an infectious agent by the study treatment, as defined below
    - 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.
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT > 10 × ULN
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine release syndrome, influenza-like illness, and systemic inflammatory response syndrome
- Nephritis
- Ocular toxicities (eg, uveitis, retinitis)
- Myositis
- Myopathies, including rhabdomyolysis
- ≥ Grade 2 cardiac disorders (eg, atrial fibrillation, myocarditis, pericarditis)
- Vasculitis

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 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 autoimmmune 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 of them may appear with a delayed onset. Diagnosis of irAEs should be based on exposure to an ICI and a reasonable immune-based mechanism of the observed AE. Whenever possible, histologic examination or other immune-based diagnostic evaluations should be used to support the diagnosis. Other etiologic causes including AEs from tumor progression should be ruled out.

The spectrum of irAEs is wide and can be general or organ-specific. Examples of general irAEs in subjects treated with ICIs are fatigue, fever, and chills. Organ-specific irAEs consist of dermatitis (rash, pruritus, vitiligo, oral mucositis, and gingivitis), enterocolitis (diarrhea with abdominal pain and clinical or radiological evidence of colonic inflammation), and endocrinopathies (pituitary, thyroid, adrenal, testes). Diagnosis of endocrine dysfunction is challenging with relatively unspecific symptoms. Additional laboratory testing of the endocrine axes may be helpful: prolactin (pituitary-hypothalamic function), 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 infiltrates periportal and surrounding primary biliary ducts) and pneumonitis (acute interstitial pneumonia). Less frequent irAEs include neurologic syndromes (myasthenia gravis, Guillian-Barré syndrome, aseptic meningitis), ocular AEs (uveitis), renal AEs (interstitial nephritis), cardiac AEs (myocarditis), muscular AEs (myositis), and pancreatic AEs (lipase increase).

Medical management of irAEs focuses on suppressing the immune response with non-steroidal and steroidal anti-inflammatory medication. Treatment algorithms for high grade irAEs have been developed and should be followed for subjects with suspected irAEs because of ICI exposure (Naidoo et al 2015).

## 8.4 Follow-Up of Adverse Events

If a subject is experiencing an ongoing treatment-related AE that led to study treatment discontinuation, SAE, or AESI at the time of the Post-Treatment Follow-Up Visit 30 (+14) days after the date of the decision to discontinue treatment (see Section 5.3 for further details), the subject will continue to be followed until either:

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

This follow-up requirement also applies to related SAEs that occur > 30 days after the date of the decision to discontinue study treatment.

In addition, AESIs are to be recorded in the CRF until 90 days after the decision to discontinue study treatment

The status of all other AEs that are ongoing 30 days after the date of the decision to discontinue study treatment will be documented as of the Post-Treatment Follow-Up Visit.

## 8.5 Other Safety Considerations

### 8.5.1 Pregnancy

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

The investigator must inform the Sponsor of the pregnancy. Forms for reporting pregnancies will be provided to the study sites upon request. The outcome of a pregnancy (for a subject or for the partner of a subject) and the medical condition of any resultant offspring must be reported to the Sponsor or designee. Any birth defect or congenital anomaly must be reported as an SAE and

any other untoward events occurring during the pregnancy must be reported as AEs or SAEs, as appropriate.

Females should not breastfeed while receiving study treatment and for the following periods after discontinuing study treatment:

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

### 8.5.2 Medication Errors/Overdose

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

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

In case of overdose, the Sponsor medical monitor or designee should be contacted promptly to discuss how to proceed. A Medication Error Notification Form should be completed and sent to the Sponsor following any suspected medication error. Any AEs that occur as a result of an overdose have to be treated according to clinical standard practice.

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

# 9 STATISTICAL CONSIDERATIONS

Details of the planned analyses, including strategies if needed to assess and address consequences of the COVID-19 pandemic on trial conduct and study data, will be documented in a separate Statistical Analysis Plan (SAP). Summaries will generally be presented by cohort/dose group and overall (total subjects). No formal statistical tests are planned for this study. Confidence intervals will be calculated for selected endpoints.

## 9.1 Power and Sample Size

### 9.1.1 Dose-Escalation Stage

The number of subjects per dose escalation cohort has been chosen based on a well-established Phase 1 dose-escalation trial design. Subjects are accrued into cohorts in a “3 plus 3” fashion with each cohort consisting initially of 3 subjects and potentially expanding to 6 subjects based upon the number of DLTs observed. A total of 9 to 36 subjects may be enrolled in this stage, depending upon the number of escalation cohorts and subjects required to establish an MTD or recommended Expansion Stage dose and schedule.

### 9.1.2 Expansion Stage

#### 9.1.2.1 Combination-Therapy Expansion Cohorts

The objective for the Combination-Therapy Expansion Cohorts is to estimate ORR to assess if the true response rate with this combination regimen is better than that expected with monotherapy. Thus, 2-sided 80% and 60% Blyth-Still-Casella CIs will be constructed for ORR, providing 90% and 80%, respectively, 1-sided confidence when interpreting the lower bound. The sample size of 30 subjects for each of the Expansion Cohorts was chosen to ensure the lower bound of the 2-sided 80% CI extended no more than 12 percentage points from the point estimate. Example 80% and 60% 2-sided CIs, with the 1-sided interpretations of the lower bound, are shown in Table 9-1 for a range of potential values for observed ORR.

**Table 9-1: Example Blyth-Still-Casella Confidence Intervals for N=30 for ORR for Expansion Cohorts with 1-Sided Interpretations of the Lower Bound**

| Observed Responses (Total N=30) | Observed ORR (%) | 80% 2-Sided CI | | | 60% 2-Sided CI | | |
|---|---|---|---|---|---|---|---|
| | | LCL (%) | UCL (%) | True ORR[a] (90% Confidence) (%) | LCL (%) | UCL (%) | True ORR[a] (80% Confidence) (%) |
| 17 | 57 | 44 | 69 | ≥ 44 | 47 | 66 | ≥ 47 |
| 15 | 50 | 38 | 62 | ≥ 38 | 41 | 59 | ≥ 41 |
| 12 | 40 | 28 | 53 | ≥ 28 | 31 | 47 | ≥ 31 |
| 11 | 37 | 25 | 50 | ≥ 25 | 28 | 44 | ≥ 28 |
| 10 | 33 | 23 | 46 | ≥ 23 | 25 | 41 | ≥ 25 |
| 9 | 30 | 19 | 42 | ≥ 19 | 24 | 38 | ≥ 24 |
| 8 | 27 | 16 | 38 | ≥ 16 | 19 | 34 | ≥ 19 |
| 7 | 23 | 15 | 34 | ≥ 15 | 16 | 31 | ≥ 16 |
| 6 | 20 | 11 | 31 | ≥ 11 | 13 | 28 | ≥ 13 |
| 5 | 17 | 9 | 28 | ≥ 9 | 12 | 24 | ≥ 12 |
| 4 | 13 | 6 | 25 | ≥ 6 | 8 | 19 | ≥ 8 |

CI, confidence interval; LCL, lower confidence limit; ORR objective response rate; UCL, upper confidence limit.

[a] Per 1-sided interpretation of the lower bound.

**Table 9-2: Example Blyth-Still-Casella Confidence Intervals for N=15 for ORR for the Expansion Cohorts of 15 Subjects with 1-Sided Interpretations of the Lower Bound**

| Observed Responses (Total N=15) | Observed ORR (%) | 80% 2-Sided CI | | | 60% 2-Sided CI | | |
|---|---|---|---|---|---|---|---|
| | | LCL (%) | UCL (%) | True ORR[a] (90% Confidence) (%) | LCL (%) | UCL (%) | True ORR[a] (80% Confidence) (%) |
| 9 | 60 | 42 | 77 | ≥ 43 | 46 | 70 | ≥ 46 |
| 7 | 47 | 28 | 64 | ≥ 28 | 33 | 61 | ≥ 33 |
| 6 | 40 | 23 | 57 | ≥ 23 | 30 | 54 | ≥ 30 |
| 5 | 33 | 20 | 51 | ≥ 20 | 23 | 46 | ≥ 23 |
| 4 | 27 | 12 | 44 | ≥ 12 | 16 | 39 | ≥ 16 |
| 3 | 20 | 10 | 36 | ≥ 10 | 11 | 33 | ≥ 11 |
| 2 | 13 | 6 | 28 | ≥ 6 | 8 | 23 | ≥ 8 |
| 1 | 7 | 1 | 23 | ≥ 1 | 3 | 16 | ≥ 3 |

CI, confidence interval; LCL, lower confidence limit; ORR objective response rate; UCL, upper confidence limit.
[a] Per 1-sided interpretation of the lower bound.

Combination-Therapy Expansion Cohorts may enroll additional subjects beyond the initial subjects per Extended Enrollment Option 1 or 2 (described below). It is anticipated that not all Expansion Cohorts will open for additional enrollment. Note: Up to 10 tumor-specific cohorts (including SAC Cohorts) may be expanded in the Expansion Stage; extended enrollment beyond 30 subjects is not allowed in the SAA Cohort.

Extended Enrollment Option 1: Should the SOC deem that a clinically meaningful ORR has been observed in an Expansion Cohort, approximately 100 new subjects may be added to that cohort to further investigate the safety and clinical benefit of the combination in that treatment setting.

Decisions by the SOC regarding the clinical significance of the achieved ORR in Expansion Cohorts will include an evaluation of the lower bound of confidence intervals for ORR in the initially enrolled approximately 30 subjects, and the expansion cohorts will be extended as follows:

Extension-Part I: Approximately 50 additional subjects will be added in this extension part for a total of approximately 80 subjects in an expansion cohort. The observed ORR in the previously enrolled subjects will be considered. A minimum observed ORR of around 20% or more will be used as a target (though not a requirement) for the SOC to consider cohort expansion. This corresponds to 80% confidence that the true ORR is ≥ 13% for n = 30 (see Table 9-1) (≥ 11% for n = 15; see Table 9-2). The magnitude of ORR deemed clinically meaningful by the SOC may vary by cohort, and the committee may consider other factors of clinical benefit (eg, time to response, duration of response, safety/tolerability) in the decision to extend enrollment.

**Table 9-3: Example Blyth-Still-Casella Confidence Intervals for N=80 for ORR for Expansion Cohorts with 1-Sided Interpretations of the Lower Bound**

| Observed Responses (Total N=80) | Observed ORR (%) | 80% 2-Sided CI | | |
|---|---|---|---|---|
| | | LCL (%) | UCL (%) | True ORR[a] (90% Confidence) (%) |
| 32 | 40 | 33 | 47 | ≥ 33 |
| 31 | 39 | 31 | 46 | ≥ 31 |
| 30 | 38 | 30 | 45 | ≥ 30 |
| 29 | 36 | 29 | 44 | ≥ 29 |
| 28 | 35 | 28 | 42 | ≥ 28 |
| 27 | 34 | 27 | 41 | ≥ 27 |
| 26 | 33 | 26 | 40 | ≥ 26 |
| 25 | 31 | 25 | 39 | ≥ 25 |
| 24 | 30 | 23 | 37 | ≥ 23 |

CI, confidence interval; LCL, lower confidence limit; ORR objective response rate; UCL, upper confidence limit.
[a] Per 1-sided interpretation of the lower bound.

Extension-Part II: Approximately 50 additional subjects will be added in this second extension part for a maximum total of approximately 130 subjects in an expansion cohort. The observed

ORR for the previously enrolled subjects (N= ~80, ~30 subjects initially enrolled + ~50 subjects enrolled in Extension-Part I) will be considered. A minimum observed ORR of around 35% or more will be used as a target for the SOC to consider additional cohort expansion. This corresponds to 90% confidence that the true ORR is ≥ 28% for n = 80 (see Table 9-3). Part II extension will only apply to tumor indications with a high-unmet medical need and very encouraging efficacy and safety data observed in Part I.

A total sample size of 130 subjects was selected to ensure the lower bound of the 95% confidence interval for ORR will extend less than 10% points from the point estimate if Part II is implemented. See Table 9-4 for confidence intervals for a range of potentially observed response rates.

**Table 9-4: Example Blyth-Still-Casella Confidence Intervals for N=130 for ORR for Expansion Cohorts with 1-Sided Interpretations of the Lower Bound**

| Observed Responses (Total N=130) | Observed ORR (%) | 95% 2-Sided CI | | |
|---|---|---|---|---|
| | | LCL (%) | UCL (%) | True ORR[a] (97.5% Confidence) (%) |
| 65 | 50 | 41 | 59 | ≥ 41 |
| 58 | 45 | 36 | 54 | ≥ 36 |
| 52 | 40 | 32 | 49 | ≥ 32 |
| 45 | 35 | 27 | 43 | ≥ 27 |

CI, confidence interval; LCL, lower confidence limit; ORR objective response rate; UCL, upper confidence limit.
[a] Per 1-sided interpretation of the lower bound.

Extended Enrollment Option 2: For Combination-Therapy Expansion Cohorts in which the initially enrolled approximately 30 subjects do not meet the criteria for Extended Enrollment Option 1, the SOC may decide to allow each selected Expansion Cohort to enroll approximately 30 new subjects to receive the highest dose level of cabozantinib explored in the Dose-Escalation Stage (60 mg) in combination with atezolizumab 1200 mg to explore whether the higher cabozantinib dose will lead to improved clinical activity and maintain an acceptable safety profile.

Details about the composition, role, schedule, and guidance for committee decisions are provided in a separate SOC Charter.

#### 9.1.2.2 Exploratory Single-Agent Cabozantinib (SAC) Cohorts

SAC Cohorts 19, 20, and 21 will each initially enroll approximately 30 subjects with UC, NSCLC, and CRPC, respectively, with an opportunity to extend enrollment with approximately 50 additional subjects in each cohort per the SOC. All analyses conducted for these cohorts will be presented for descriptive purposes. No formal comparisons to other study cohorts are planned. Median duration and corresponding 95% CI will be estimated using Kaplan-Meier method for PFS and OS. Objective response rate will also be estimated. Descriptive statistics such as frequency and percent will be presented for safety endpoints described in Section 9.3.1.

#### 9.1.2.3 Exploratory Single-Agent Atezolizumab (SAA) Cohort

SAA Cohort 22 will initially enroll 10 subjects with advanced CRPC. Additional enrollment will be conditional upon responses observed among the first 10 enrolled subjects. If there are at least two confirmed responses (PR or CR) per RECIST 1.1 among the initial 10 subjects enrolled, up to 20 additional subjects may be enrolled for a maximum total of 30 subjects. Extended enrollment beyond 30 subjects is not allowed in this cohort. All analyses conducted for this cohort will be presented for descriptive purposes. No formal comparisons to other study cohorts are planned. Median duration and corresponding 95% CI will be estimated using Kaplan-Meier method for PFS and OS. Objective response rate will also be estimated. Descriptive statistics such as frequency and percent will be presented for safety endpoints described in Section 9.3.1.

#### 9.1.2.4 Second Agent Add-On Stage

All analyses conducted for subjects treated in the Second Agent Add-On Stage will be presented for descriptive purposes. No formal comparisons to other study cohorts are planned. Radiographic endpoints will be assessed relative to the new baseline established at entry to the Single Agent Add-On Stage. Median duration and corresponding 95% CI will be estimated using Kaplan-Meier method for PFS. Objective response rate will also be estimated. Descriptive statistics such as frequency and percent will be presented for safety endpoints described in Section 9.3.1.

### 9.2 Analysis Populations

#### 9.2.1 Safety Population

The Safety population will consist of all subjects who received any study treatment. As enrollment is defined by receipt of study treatment, an Enrolled population is not defined to be distinct from the Safety population.

#### 9.2.2 Dose-Escalation Population

The Dose-Escalation population will include subjects who were not replaced per Section 3.9.

### 9.2.3 Other Population(s)

Additional analysis populations may be defined in the SAP.

## 9.3 Planned Analyses

### 9.3.1 Safety and Tolerability Analyses

Safety will primarily be assessed by the evaluation of AEs and laboratory tests. Tolerability will be assessed by evaluation of study treatment modification and discontinuation.

#### 9.3.1.1 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 v4 and will judge each event to be "not related" or "related" to study treatment. Adverse events leading to study treatment discontinuation will also be judged by the investigator to be causally associated, or not, with the disease under study.

Summaries of AEs, irAEs, AESIs, and SAEs will be tabulated by cohort according to system organ class and preferred term by overall incidence; worst reported severity; and relationship to study treatment.

At each level of summarization, a subject will be counted only once for each AE preferred term he or 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.

A narrative will also be prepared to describe the accrual and expansion of Dose-Escalation Stage cohorts, subject replacement, the DLTs observed, Cohort Review Committee decisions and the final rationale for the recommended Expansion Stage dose.

#### 9.3.1.2 Laboratory Test Results

Selected laboratory test results will be summarized by treatment group to evaluate worst post-baseline CTCAE grade and shifts or changes from baseline.

#### 9.3.1.3 Study Treatment

Study treatment parameters will be presented separately for each agent, cabozantinib and atezolizumab. The number of subjects experiencing dose reduction, delay, interruption, modification and/or discontinuation due to adverse event will be provided as appropriate for each

agent. Duration and intensity of study treatment will also be tabulated. Data for the SAC Cohorts, SAA Cohort, and Second Agent Add-On Stage will be summarized separately as described in Sections 9.1.2.2, 9.1.2.3, and 9.1.2.4, respectively.

### 9.3.2 Analyses of Preliminary Antitumor Activity

The objective of the combination therapy in the Expansion Stage is to estimate ORR, defined as the proportion of subjects with a confirmed CR or PR per RECIST 1.1 as determined by the investigator. Similarly, ORR will be determined per irRECIST for immune response (Appendix H) as determined by the investigator as an exploratory endpoint. ORR will be evaluated independently within each of the Expansion Cohorts and within the dose-escalation cohorts. For selected Expansion Stage cohorts, ORR per RECIST 1.1 will also be evaluated per BIRC.

Best overall tumor response, based upon the evaluation of target, non-target, and new lesions, will be presented as the proportion of subjects in each of the following categories: CR, PR, SD, PD, and not evaluable, and include the ORR. In the Expansion Cohorts, 2-sided 80% and 60% Blyth-Still-Casella CIs will be presented for ORR, providing 90% and 80% 1-sided confidence when interpreting the lower bound for the purpose of evaluating preliminary efficacy of combination therapy vs. expected efficacy with single-agent treatment from historical studies. Confidence intervals at the 95% level will also be presented for consistency with standard presentation conventions.

For exploratory purposes, the ORR as assessed by investigator per RECIST 1.1 will be presented descriptively for each dose-escalation cohort.

Median PFS and OS with associated 2-sided 95% CIs will be estimated using Kaplan-Meier methods.

Duration of response is defined as the time from first documented objective response (CR or PR) as is assessed by the investigator that is subsequently confirmed until the earlier of radiographic progression or death, or censoring due to lack of these events or start of nonprotocol anticancer therapy. Medians and confidence intervals will be estimated using Kaplan-Meier analysis, limited to patients who experienced a confirmed objective response.

### 9.3.3 Interim Analyses

Prior to Protocol Amendment 2.0, the Cohort Review Committee reviewed accumulating data from the Dose-Escalation cohorts as described in Section 12.1.

No formal interim analyses are planned for the cohorts in the Expansion Stage. However, safety and anti-tumor findings will be reviewed on an ongoing basis.

# 10 OTHER ANALYSES

## 10.1 Pharmacokinetic Analyses

The plasma concentration of cabozantinib will be analyzed by the Sponsor or designee using a validated bioanalytical method. Descriptive statistics (eg, number, mean and/or median, standard deviation, and coefficient of variation) will be used to describe the concentration-time data. Where appropriate, these data may be analyzed using population PK models and/or combined with data from other studies as part of a meta-analysis. The influence of exposure on biomarkers, clinical safety parameters (eg, selected AEs) or clinical response may also be explored.

Serum concentrations of atezolizumab will be analyzed by Sponsor designated lab using validated enzyme-linked immunosorbent assay (ELISA). Descriptive statistics (eg, number, mean and/or median, standard deviation, and coefficient of variation) will be used to summarize the concentration-time data per visit.

## 10.2 Immunogenicity Analyses

Results of anti-drug antibody (ADA) testing (ie, immunogenicity testing) will be summarized overall as the number of subjects with ADA at any time point. The association between human ADA incidence, PK, and efficacy and/or safety outcomes may be explored.

## 10.3 Biomarker Analyses

Analyses that may include MET and PD-L1 expression levels and potential correlation with clinical response and other analyses (eg, tumor mutational burden) will be summarized. Exploratory evaluation of relevant biomarkers for on-target effects of therapy and tumor and/or peripheral changes in immune response may be summarized separately.

# 11 DATA QUALITY ASSURANCE

Accurate and reliable data collection will be ensured by verification and cross-check of the CRFs against the investigator’s records by the study monitor (source document verification) and by the maintenance of a drug–dispensing log by the investigator. Data collected on paper CRFs, if any, will be entered into a computer database. If electronic CRFs are employed, authorized study site personnel will enter data directly into a computer database. Study databases will be subject to electronic and manual quality assurance procedures.

# 12 STUDY COMMITTEES

## 12.1 Cohort Review Committee

The Cohort Review Committee included the Sponsor medical monitor and/ or the Sponsor Drug Safety physician, the Sponsor's chief medical officer (or Vice President of Clinical Development), and participating principal investigators. The Cohort Review Committee reviewed all safety and available PK data from all subjects from each cohort. All available safety and PK data was considered in decisions to dose escalate or de-escalate the next cohort or to expand the current cohort in the Dose-Escalation Stage. Once all subjects in the Dose-Escalation Stage completed the DLT Evaluation Period, the Cohort Review Committee determined the MTD/recommended dose and dosing schedule for the Expansion Stage based on review and discussion of the safety and available PK data from all subjects in the Dose-Escalation Stage. Details about this process are provided in Section 3.5.1.

## 12.2 Study Oversight Committee

The SOC consists of Sponsor medical, safety, and biostatistical personnel and selected investigators which are experts in the treatment of the enrolled tumor types. The SOC will periodically monitor safety and efficacy data of cohorts in the Expansion Stage and decide upon further enrollment extension of up to 10 cohorts (excluding the SAA Cohort) as described in Section 9.1.2.

Details about the composition, role, schedule, and guidance for committee decisions are provided in a separate SOC Charter.

## 12.3 Executive Safety Committee

The Sponsor's ESC is established to ensure a review of safety data from clinical trials and post-marketing exposure is performed at least on a quarterly basis. The ESC is managed by the Head of Benefit-Risk Management, and includes the following members: ESC Chair, Senior Vice President of Drug Safety, Chief Medical Officer, Vice President of Clinical Development, and qualified representatives of other functional groups as appropriate.

## 12.4 Blinded Independent Radiology Committee (BIRC)

A BIRC will be established to evaluate tumor scans and prior radiation/prior local tumor history data of trial subjects for selected Expansion Stage cohorts in a central, blinded, and independent fashion. The BIRC will comprise 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.

# 13 ETHICAL ASPECTS

## 13.1 Local Regulations

The study must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" (GCP) ICH E6 Tripartite Guideline (January 1997) and remain consistent with the most recent version of the Declaration of Helsinki. The investigator will ensure that the conduct of the study complies with the basic principles of GCP as outlined in the current version of 21 CFR, subpart D, Part 312, "Responsibilities of Sponsors and Investigators" Part 50, "Protection of Human Subjects" and Part 56, "Institutional Review Boards."

## 13.2 Informed Consent

Sample informed consent forms (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

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

Protocol modifications may be made and will be prepared, reviewed, and approved by the Sponsor representatives.

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

## 15 CONDITIONS FOR TERMINATING THE STUDY

The Sponsor reserves the right to terminate the study, and investigators reserve the right to terminate their participation in the study, at any time. Should this be necessary, the Sponsor and the investigator will arrange the procedures on an individual study basis after review and consultation. In terminating the study, the Sponsor and the investigator will ensure that adequate consideration is given to the protection of the subjects' interests.

Study Completion by Country or by Site: After sufficient data have been collected to adequately evaluate all study endpoints and upon site notification by the Sponsor, the study will be considered complete at sites and in countries that no longer have active subjects.

# 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 (usually predefined by the project 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 retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by the Sponsor or designee, whichever is longer. The investigator must contact the Sponsor prior to destroying any records associated with the study. The Sponsor or designee will notify the investigator when the study records are no longer needed. If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, study site, IRB). Notice of such transfer will be given in writing to the Sponsor or designee.

If the investigator cannot guarantee the archiving requirement 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 supply the sponsor with any required background data from the study documentation or clinic records. This is particularly important when CRFs (if paper) are illegible or when errors in data transcription are suspected. In case of special problems or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

## 16.3 Audits and Inspections

The investigator should understand that source documents for this study must be made available, after appropriate notification, to qualified personnel from the Sponsor's Quality Assurance Unit (or designee) or to health authority inspectors. The verification of the CRF data must be by direct inspection of source documents.

## 16.4 Case Report Forms

The term "case report form" includes as applicable paper forms and/or electronic data capture screens or forms for studies that utilize electronic data capture. For enrolled subjects, all and only data for the procedures and assessments specified in this protocol and required by the CRFs are to be submitted on the appropriate CRF (unless source data are transmitted to the Sponsor or a designee electronically, eg, central laboratory data). Data from some procedures required by the protocol, such as physical examinations, will be recorded only on the source documents and will not be transcribed to CRFs. Additional procedures and assessments may be performed as part of the investigator's institution or medical practice standard of care. Data from assessments associated with the follow-up of AEs are to be recorded on unscheduled CRF pages. Otherwise, data for unscheduled or additional assessments are to remain in the subject's medical record and are not to be recorded on CRFs unless specifically requested.

The CRF (paper or electronic) 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.

All paper forms are to be typed or filled out using indelible ink and must be legible. Errors are to be crossed out but not obliterated, the correction inserted, and the change initialed and dated by the investigator or his or her authorized delegate. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor in the CRF and in all required reports.

The Sponsor's data management personnel (or designees) may, in specific circumstances, modify study data – without changing the meaning of the data – to ensure the dataset complies with conventions required for successful data extract, thesaurus coding, or uniform reporting and does not cause these processes to fail. Examples of these administrative changes include:

- Substitution of non-standard ASCII characters (codes 128-255) or deletion of carriage returns (code 13) that are incompatible with the SAS XPT file format (eg, accented letters replaced with non-accented ones; e for é)
- Splitting multiple verbatim AE terms into multiple records (eg, "nausea and vomiting" to separate records for "nausea" and "vomiting")
- Reformatting failed eligibility criteria numbers for uniformity or specificity (eg, changing "2 a" to "2A"; or "2" to "2A" based on corroborating evidence from the clinical database)
- Changing cause of death from "unknown" to "unknown cause of death" to facilitate coding in the MedDRA thesaurus

Such changes follow a pre-defined documented process and can be clearly identified in the database audit trial. By participating in this study, investigators agree that such administrative changes are permissible without their specific prior approval. A list of all specific changes made can be provided to investigators upon request at any time.

## 17 MONITORING THE STUDY

The responsible Sponsor monitor (or designee) will contact and visit the investigator regularly and will be allowed on request to inspect the various records of the trial (CRFs and other pertinent data), provided that subject confidentiality is maintained in accordance with local requirements.

It will be the monitor's responsibility to inspect the CRFs at regular intervals throughout the study to verify both adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor is to have access to laboratory test reports and other subject records needed to verify the entries on the CRF. The investigator (or designee) must agree to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

## 18 CONFIDENTIALITY OF TRIAL DOCUMENTS AND SUBJECT RECORDS

The investigator must assure that subjects' anonymity will be maintained and that their identities are protected from unauthorized parties. On CRFs or other documents submitted to the Sponsor or designees, subjects are to be identified by identification codes and not by their names. The investigator should keep a subject enrollment log showing codes, names, and addresses. The investigator must maintain documents not for submission to the Sponsor or designees (eg, subjects' written consent forms) in strict confidence.

All tumor scans, research samples, photographs, and results from examinations, tests, and procedures may be sent to the Sponsor and its partners or designees for review.

## 19 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

The results of this study may be published or presented at scientific meetings. The investigator agrees to submit all manuscripts or abstracts to the Sponsor for review at least 30 days before submission. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In the event that the Sponsor coordinates a publication or presentation of study results from all study sites, the participation of the investigator(s) or other representatives of the study site(s) as named author(s) shall be determined in accordance with Sponsor policy. Authorship will be assigned in accordance with contribution to design, execution, and interpretation and analysis of the study.

The Sponsor may, at its sole option, provide funding to support the development, submission, and/or presentation of publications for scientific/medical journals or conferences. For publications coordinated by the Sponsor, the Sponsor may also provide funding to support travel and conference registration for the presenting author to attend the conference for the sole purpose of presenting the publication.

# 20 COMPLIANCE WITH DATA PROTECTION LAWS

The conduct of this study and the processing of any personal data collected from each subject (or from a subject's healthcare professional or other relevant third-party sources) by the Sponsor, the site, and the Investigator for use in the study will fully adhere to the requirements set out in applicable data protection and medical privacy laws or regulations, including, without limitation, the General Data Protection Regulation ([EU] 2016/679) and any national implementing laws, regulations, and secondary legislation, as amended or updated from time to time. The Sponsor shall ensure that at all times it has an appropriate legal basis for processing personal data under applicable data protection law (which may include consent from the subject or another lawful basis).

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## Appendix A: Schedule of Assessments for the Dose-Escalation Stage

The schedules of required assessments for the Dose-Escalation Stage are presented in this appendix (Table A-1).

Most study assessments and procedures (including treatment administration) will be performed in cycles. Cycle 1 Day 1 (C1D1) is defined as the date of first dose of any study treatment. A cycle is generally the 21-day interval starting with the date of an atezolizumab infusion and ending with the day before the next atezolizumab infusion. However, under some circumstances no atezolizumab may be dosed during a cycle:

- If atezolizumab treatment is discontinued but cabozantinib treatment is allowed to continue with the notification of the Sponsor, each consecutive 21-day interval starting with the date of the decision to discontinue atezolizumab will be defined as a cycle. If the decision to discontinue atezolizumab occurs less than 21 days after the last infusion, then the next cycle will begin on the 22$^{nd}$ day after the last infusion.

Cycles may extend beyond 21 days if atezolizumab dosing is delayed. During an atezolizumab dose delay, subjects should return to the site for scheduled safety visits every three weeks from the last dose of atezolizumab. Further, the study site should perform unscheduled visits or telephone calls weekly (or more frequently) as clinically indicated to monitor subject safety and appropriateness for re-treatment with study treatment. Other unscheduled visits are permitted whenever necessary. See Section 5.5 for further details.

Imaging assessments (CT, MRI, bone scan) are to be performed at protocol-defined, fixed intervals based the first dose of study treatment (defined as Week 1 Day 1 [W1D1]); all subsequent time points for these assessments will apply the same nomenclature, which will not be modified as a result of modifications or discontinuations of treatment administration.

Unless otherwise indicated, in the absence of side effects all scheduled visits will occur within windows for the protocol-specified visit schedule. If the subject experiences side effects, study treatment can be modified or delayed as described in Section 6.5. If the subject is unable to have a study assessment taken within the defined time window due to an event outside of his or her control (eg, clinic closure, personal emergency, inclement weather, vacation), the assessment should be performed as close as possible to the required schedule. Special accommodations during the global COVID-19 pandemic are described in Appendix M. Laboratory panels for serum chemistry, hematology, and urinalysis are defined in Section 5.6.5.

## Table A-1: Schedule of Assessments for the Dose-Escalation Stage: *Standard Dosing Schedule*

| | Pre-enrollment | Post-enrollment | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cycle 1 (± 3 days) | | | Cycle 2 (± 3 days) | | | | | | |
| **Assessment:** | **Screening[a] (Before First Dose)** | **Day 1** | **Day 10** | **Day 21** | **Day 1** | **Day 10** | **Day 21** | **Cycles 3-8 (± 3 days)** | **Cycles 9 and above (± 5 days)** | **30-Day Post-Treatment Follow-Up (+14 days)** | **Extended Follow Up** |
| Informed consent (Section 5.1) | X[b] | | | | | | | | | | |
| Demographics, medical and cancer history (Section 5.6.1) | ≤ 28 days | | | | | | | | | | |
| Physical examination[c] + weight (Section 5.6.2) | ≤ 28 days | X predose | X | X | X[d] | | | Day 1 of every cycle or every three weeks after the last dose of atezolizumab (if infusions are delayed), whichever is earlier. | | X | |
| ECOG PS (Section 5.6.2, Appendix F) | ≤ 28 days (+ Karnofsky PS for RCC subjects) | X | X | X | X[d] | | | Day 1 of every cycle or every three weeks after the last dose of atezolizumab (if infusions are delayed), whichever is earlier. | | X | |
| Vital signs (Section 5.6.3) | ≤ 28 days | X[e] | X | X | X[e] | | | Day 1 of every cycle or every three weeks after the last dose of atezolizumab (if infusions are delayed)[e], whichever is earlier. | | X | |
| 12-lead ECG (Section 5.6.4)[f] | ≤ 14 days | X[g] predose | | X | X[d] | | | Day 1 of every 4th cycle starting with C3D1 (ie, C3D1, C7D1, etc) or every 12 weeks after the last dose of atezolizumab (if infusions are delayed), whichever is earlier. | | X | |
| Hematology and chemistry by central lab (Section 5.6.5) | ≤ 14 days | X[h,i] predose | X | X | X[h,i] predose | | | Day 1 of every cycle or every three weeks after the last dose of atezolizumab (if infusions are delayed)[h,i]whichever is earlier. | | X | |
| Hepatitis screening[j] by central lab (Section 5.6.5) | X | | | | | | | | | | |
| PT/INR and PTT by central lab (Section 5.6.5) | ≤ 14 days | X[g] predose | | X | X[d] | | | Day 1 of every 3rd cycle starting with C3D1 (ie, C3D1, C6D1, etc) or every nine weeks after the last dose of atezolizumab (if infusions are delayed), whichever is earlier. | | X | |
| Urinalysis by **local** lab (Section 5.6.5) | ≤ 14 days | X[g,h] predose | | X | X[h] predose | | | Day 1 of every cycle or every three weeks after the last dose of atezolizumab (if infusions are delayed)[h], whichever is earlier. | | X | |

## Table A-1: Schedule of Assessments for the Dose-Escalation Stage: *Standard Dosing Schedule*

| | Pre-enrollment | Post-enrollment | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cycle 1 (± 3 days) | | | Cycle 2 (± 3 days) | | | | | | |
| **Assessment:** | **Screening[a] (Before First Dose)** | **Day 1** | **Day 10** | **Day 21** | **Day 1** | **Day 10** | **Day 21** | **Cycles 3-8 (± 3 days)** | **Cycles 9 and above (± 5 days)** | **30-Day Post-Treatment Follow-Up (+14 days)** | **Extended Follow Up** |
| Urine chemistry incl. UPCR by central lab (Section 5.6.5) | ≤ 14 days | X[g] predose | | X | X[d] | | | Day 1 of every other cycle starting with C3D1 (ie, C3D1, C5D1, etc) or every six weeks after the last dose of atezolizumab (if infusions are delayed), whichever is earlier. | | X | |
| Pregnancy test by **local** lab (Section 5.6.5) | ≤ 7 days serum | X[g] predose (serum) | | | X (serum or urine) | | | Day 1 of every cycle or every three weeks after the last dose of atezolizumab (if infusions are delayed). (serum or urine), whichever is earlier. | | X | |
| Thyroid function test by central lab (Section 5.6.5) | ≤ 14 days | X[g] predose | | X | X[d] | | | Day 1 of every 3rd cycle starting with C3D1 (ie, C3D1, C6D1, etc) or every nine weeks after the last dose of atezolizumab (if infusions are delayed), whichever is earlier. | | X | |
| Archival tumor tissue sample[k] (Section 5.6.8) | X | | | | | | | | | | |
| Tumor assessment: CT/MRI **Chest, Abdomen, Pelvis** (Section 5.6.9) | ≤ 28 days | CT of the chest, abdomen, and pelvis or CT of the chest with MRI of the abdomen and pelvis will be performed in all subjects at screening and every 6 weeks (± 5 days) after first dose (at W7D1, W13D1 etc). Upon completion of 12 months on study, these assessments will be performed every 12 weeks (± 7 days). To ensure image consistency, the same imaging modalities and acquisition protocols used at screening are to be used for subsequent tumor assessments.<br>CT/MRIs are to be performed per the protocol-defined schedule regardless of whether study treatment is reduced, interrupted, delayed, or discontinued, and the tumor assessment schedule is independent of the atezolizumab dosing schedule. Tumor imaging will continue until radiographic disease progression per RECIST 1.1 as determined by the investigator. For subjects who discontinue study treatment before radiographic disease progression per RECIST 1.1, regularly scheduled imaging assessments should continue if possible until radiographic progression per RECIST 1.1 or initiation of subsequent anticancer therapy.<br>PR or CR per RECIST 1.1 at a given time point must be confirmed by repeat assessments ≥ 4 weeks after the criteria for response are first met. Subjects with PD per RECIST 1.1 who continue with study treatment are to have tumor measurement outcomes confirmed ≥ 4 weeks after the initial PD criteria were met. For subjects who continue treatment after the confirmatory tumor scans, regularly scheduled imaging will continue. | | | | | | | | | |

## Table A-1: Schedule of Assessments for the Dose-Escalation Stage: *Standard Dosing Schedule*

| | Pre-enrollment | Post-enrollment | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cycle 1 (± 3 days) | | | Cycle 2 (± 3 days) | | | | | | |
| **Assessment:** | **Screening[a] (Before First Dose)** | **Day 1** | **Day 10** | **Day 21** | **Day 1** | **Day 10** | **Day 21** | **Cycles 3-8 (± 3 days)** | **Cycles 9 and above (± 5 days)** | **30-Day Post-Treatment Follow-Up (+14 days)** | **Extended Follow Up** |
| Tumor assessment: MRI/CT **Brain** (Section 5.6.9) | ≤ 28 days | MRI (or CT) of the brain will be performed at screening in all subjects with RCC, and for subjects with UC who have a history or clinical symptoms of brain metastasis. After first dose, MRI (or CT) scans of the brain are only required in subjects with documented, treated brain metastasis. Assessments will be performed every 12 weeks (± 7 days) after first dose (at W13D1, W26D1 etc). The schedule for these assessments is independent of the atezolizumab dosing schedule. To ensure image consistency, the same imaging modalities and acquisition protocols used at screening are to be used for subsequent tumor assessments. (Note: in order to meet the eligibility requirements of the study, brain metastasis must have been treated and stable for at least 4 weeks before first dose of study treatment. Subjects without documented brain metastasis during the screening assessment are not required to undergo brain imaging after starting treatment unless clinically indicated).<br>CT/MRIs are to be performed per the protocol-defined schedule regardless of whether study treatment is reduced, interrupted, delayed, or discontinued, and the tumor assessment schedule is independent of the atezolizumab dosing schedule. Tumor imaging will continue until radiographic disease progression per RECIST 1.1 as determined by the investigator. For subjects who discontinue study treatment before radiographic disease progression per RECIST 1.1, regularly scheduled imaging assessments should continue if possible until radiographic progression per RECIST 1.1 or initiation of subsequent anticancer therapy | | | | | | | | |
| Bone scans (Section 5.6.9) | ≤ 28 days | Technetium bone scans (TBS) will be performed at screening on subjects who have a history or clinical symptoms (ie, bone pain) of bone metastases. After study treatment initiation bone scans are only required in subjects with documented bone lesions or if clinically indicated by signs and symptoms suggestive of new bone metastases. Assessments after the first dose will follow routine clinical practice (approximately every 12 weeks throughout the first 12 months and every 24 weeks thereafter). The schedule for these assessments is independent of the atezolizumab dosing schedule. Bone scan findings alone cannot be used for the determination of progression or response in this study and need to be corroborated by CT/MRI. Bone lesions corroborated by CT/MRI must be reported as non-target or new lesions. PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. Bone scan evaluations will end on the date of last CT/MRI scan. If the bone scan schedule does not coincide with the last CT/MRI scan, no additional bone scan is needed after the last CT/MRI has been performed. | | | | | | | | |
| PK blood samples[l] (Section 5.6.6.1) | | C1D1 (before treatment, approximately 5 min after atezolizumab infusion & 2 h, 4 h, and 6-8 h after cabozantinib dose) and predose on C1D10, C2D1, and C3D1. | | | | | | | | | |
| Blood sample–Pharmacogenetic (Section 5.6.7) | | X predose | | | | | | | | | |
| Blood sample–immune cell profiling by FACS (Section 5.6.8) | | Predose on C1D1, C1D10, and C2D1 (may be performed at selected sites) | | | | | | | | | |
| Blood sample–serum/ plasma biomarkers (Section 5.6.8) | | Predose on C1D1, C1D10, C2D1, and C3D1.<br>An optional sample may be collected at the first sign of progression per the investigator. | | | | | | | | | |
| Blood sample–cell and/or plasma pharmacogenomics (Section 5.6.8) | | Predose on C1D1, C1D10, C2D1, and C3D1.<br>An optional sample may be collected at the first sign of progression per the investigator. | | | | | | | | | |

## Table A-1: Schedule of Assessments for the Dose-Escalation Stage: *Standard Dosing Schedule*

| | Pre-enrollment | Post-enrollment | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cycle 1 (± 3 days) | | | Cycle 2 (± 3 days) | | | | | | |
| **Assessment:** | **Screening[a] (Before First Dose)** | **Day 1** | **Day 10** | **Day 21** | **Day 1** | **Day 10** | **Day 21** | **Cycles 3-8 (± 3 days)** | **Cycles 9 and above (± 5 days)** | **30-Day Post-Treatment Follow-Up (+14 days)** | **Extended Follow Up** |
| Concomitant medication (Section 7) | Document concomitant medication taken from 28 days before first dose of study treatment through 30 days after the date of the decision to discontinue study treatment | | | | | | | | | | |
| Adverse events (Sections 8.1, 8.2, and 8.3.1) | Document new or worsening AEs from informed consent through 30 days (90 days for AESIs) after the date of the decision to permanently discontinue study treatment in source documents. AE information will be collected at study visits and may also be collected at any time over the phone or by spontaneous subject report. See the CRF Completion Guidelines for instructions on entering these data on Medical History and/or AE CRFs and Section 8.2 for SAE reporting requirements.<br><br>At the date of the first dose of study treatment, AEs will be documented pre- and post-dose. Certain AEs and all SAEs that are ongoing at the time of the Post-Treatment Follow-Up Visit 30 (+14) days after the date of the decision to permanently discontinue study treatment are to be followed until resolution or determination by the investigator that the event is stable or irreversible (see Section 8.4). | | | | | | | | | | |
| Atezolizumab dosing[m] (Section 6.2) | | X | | | X | | | Atezolizumab will be administered as an IV infusion at the clinic every 3 weeks (-2 days) on Day 1 of each cycle until study treatment is discontinued. | | | |
| Cabozantinib dosing (Section 6.2) | | Cabozantinib will administered in clinic C1D1 and then will be taken once daily at home until study treatment is discontinued | | | | | | | | | |
| Cabozantinib daily dosing diary (Section 5.6.10) | | The amount of cabozantinib treatment taken is to be recorded daily from C1D1 to C1D21. | | | | | | | | | |
| Dispense/return of cabozantinib and compliance accounting[n] (Section 6.3) | | Cabozantinib is to be dispensed to subjects every 3 weeks. | | | | | | | | | |

## Table A-1: Schedule of Assessments for the Dose-Escalation Stage: *Standard Dosing Schedule*

| | Pre-enrollment | Post-enrollment | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cycle 1 (± 3 days) | | | Cycle 2 (± 3 days) | | | | | | |
| **Assessment:** | **Screening[a] (Before First Dose)** | **Day 1** | **Day 10** | **Day 21** | **Day 1** | **Day 10** | **Day 21** | **Cycles 3-8 (± 3 days)** | **Cycles 9 and above (± 5 days)** | **30-Day Post-Treatment Follow-Up (+14 days)** | **Extended Follow Up** |
| Additional anticancer treatment and survival status (Sections 5.3 and 5.6.11) | | | | | | | | | | | Every 12 weeks (± 14 days) after 30-day post-treatment follow-up visit until death |

[a] Results of screening assessments must be reviewed before first dose of study treatment to confirm that the subject meets the eligibility criteria.

[b] Informed consent may be obtained greater than 28 days prior to first dose of study treatment, 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] Symptom-directed physical examination will be conducted on C1D1 before first dose of study treatment and at subsequent safety assessment visits.

[d] Assessments scheduled for C2D1 do not need to be performed if the same assessment was performed within 3 days at the end of Cycle 1.

[e] Vital signs should be assessed within 60 min prior to initiation of atezolizumab infusions, and further vital sign assessment should be performed during and after the infusion as clinically indicated.

[f] Additional ECGs are to be performed if clinically indicated.

[g] This assessment is intended to confirm suitability for treatment after screening and prior to first dose on C1D1. If this assessment has been performed during screening within 14 days (7 days for pregnancy test) prior to C1D1, this assessment does not need to be performed on C1D1 unless the subject's clinical status has changed (eg, onset of new symptoms indicative of clinical deterioration). If the assessment is performed on C1D1, the results must be available to and reviewed by the investigator prior to any treatment being administered.

[h] Serum chemistry, hematology, and urinalysis laboratory samples must be collected and the results must be reviewed within 72 h before any atezolizumab infusion administered on study.

[i] Local laboratory assessments for these panels may be obtained and used if the results are required by the investigator in a rapid timeframe. See Section 5.6.5 and the Laboratory Manual for more detailed information on laboratory assessments.

[j] Hepatitis B surface antigen and Hepatitis C antibody (with reflex testing HCV RNA if antibody test is positive) to be assessed at screening.

[k] Tumor tissue (archival) will be obtained prior to first dose whenever available. Formalin-fixed paraffin embedded (FFPE) tumor blocks are preferred but in cases where this is not possible, tumor slides should be obtained. See Translational Medicine Laboratory Manual for specific instructions.

[l] After C1D1, PK samples should be collected approximately 8 or more hours after the previous dose of cabozantinib, and if cabozantinib will be administered on that day, PK samples should be collected prior to cabozantinib administration. The investigator will ask the subject for the date and time of the most recent prior dose of cabozantinib, and this information will be recorded on the appropriate CRF page.

[m] Atezolizumab doses are not to be administered less than 19 days apart.

[n] In exceptional circumstances (eg, COVID-19 pandemic), alternative methods of distribution of oral treatment to subjects may be considered in accordance with the study site's local policies and all applicable regulations.

## Appendix B: Schedule of Assessments for the Expansion Stage (Combination-Therapy Cohorts, Exploratory Single-Agent Cabozantinib [SAC] Cohorts, and Exploratory Single-Agent Atezolizumab [SAA] Cohort)

The schedule of required assessments for the Combination-Therapy Expansion Cohorts, SAC Cohorts, and SAA Cohort is presented in this appendix in the table below.

Most study assessments and procedures (including treatment administration) will be performed in cycles. Cycle 1 Day 1 (C1D1) is defined as the date of first dose of any study treatment.

Cycles for the Expansion Cohorts: Cycles may extend beyond 21 days if atezolizumab dosing is delayed. A cycle is generally the 21-day interval starting with the date of an atezolizumab infusion and ending with the day before the next atezolizumab infusion. However, if atezolizumab treatment is discontinued but cabozantinib treatment is allowed to continue with the notification of the Sponsor, each consecutive 21-day interval starting with the date of the decision to discontinue atezolizumab will be defined as a cycle. If the decision to discontinue atezolizumab occurs less than 21 days after the last infusion, then the next cycle will begin on the 22$^{nd}$ day after the last infusion. The date of the decision to discontinue study treatment is defined for each subject as the later of (a) the date of the decision of the investigator to permanently discontinue study treatment or (b) the date of the last dose of study treatment taken by the subject.

During an atezolizumab dose delay, subjects should return to the site for scheduled safety visits every three weeks from the last dose of atezolizumab. Further, the study site should perform unscheduled visits or telephone calls weekly (or more frequently) as clinically indicated to monitor subject safety and appropriateness for re-treatment with study treatment. Other unscheduled visits are permitted whenever necessary. See Section 5.5 for further details.

Cycles for the Exploratory SAC Cohorts: The first cycle is the 21-day interval starting with the date of first dose of cabozantinib treatment. Subsequent cycles will each be exactly 21 days long, irrespective of whether cabozantinib treatment is being interrupted at the end of the cycle.

Cycles for the Exploratory SAA Cohort: A cycle is generally the 21-day interval starting with the date of an atezolizumab infusion and ending with the day before the next atezolizumab infusion.

Subjects in SAC or SAA cohorts who experience Investigator-assessed radiographic progression per RECIST 1.1 may be eligible to receive combination therapy with cabozantinib and atezolizumab. Eligibility requirements for these subjects are provided in Appendix C. The schedule of assessments in this appendix no longer applies to the eligible subjects who subsequently receive combination treatment in the Second Agent Add-On Stage; instead, refer to the schedule of assessments in Appendix C for those subjects.

Imaging assessments (CT, MRI, bone scan) are to be performed at protocol-defined, fixed intervals based on the first dose of study treatment (defined as Week 1 Day 1 [W1D1]); all subsequent time points for these assessments will apply the same nomenclature, which will not be modified as a result of modifications or discontinuations of treatment administration.

Unless otherwise indicated, in the absence of side effects all scheduled visits will occur within windows for the protocol-specified visit schedule. If the subject experiences side effects, study treatment can be modified or delayed as described in Section 6.5. If the subject is unable to have a study assessment taken within the defined time window due to an event outside of his or her control (eg, clinic closure, personal emergency, inclement weather, vacation), the assessment should be performed as close as possible to the required schedule. Special accommodations during the global COVID-19 pandemic are described in Appendix M. Laboratory panels for serum chemistry, hematology, and urinalysis are defined in Section 5.6.5.

## Appendix B: Schedule of Assessments for the Expansion Stage (Combination-Therapy Cohorts, Exploratory Single-Agent Cabozantinib [SAC] Cohorts, and Exploratory Single-Agent Atezolizumab [SAA] Cohort)

| | Pre-enrollment | Post-enrollment | | | | |
|---|---|---|---|---|---|---|
| **Assessment:** | **Screening[a] (Before First Dose)** | **Cycle 1 (± 3 days)** | **Cycles 2 through 8 (± 3 days)** | **Cycles 9 and Above (± 5 days)** | **30-Day Post-Treatment Follow-Up (+14 days)** | **Extended Follow Up** |
| Informed consent (Section 5.1) | X[b] | | | | | |
| Demographics, medical and cancer history (Section 5.6.1) | ≤ 28 days | | | | | |
| Physical examination[c] + weight (Section 5.6.2) | ≤ 28 days (with height) | C1D1 (predose) | Day 1 of every cycle or every three weeks after the last dose of atezolizumab (if infusions are delayed), whichever is earlier. | | X | |
| ECOG Performance status (Section 5.6.2, Appendix F) | ≤ 28 days (+ Karnofsky for RCC subjects) | C1D1 | Day 1 of every cycle or every three weeks after the last dose of atezolizumab (if infusions are delayed), whichever is earlier. | | X | |
| Vital signs (Section 5.6.3) | ≤ 28 days | C1D1[d] | Day 1 of every cycle or every three weeks after the last dose of atezolizumab (if infusions are delayed)[d], whichever is earlier. | | X | |
| 12-lead ECG (Section 5.6.4)[e] | ≤ 14 days | C1D1[f] predose | Day 1 of every 4th cycle starting with C3D1 (ie, C3D1, C7D1, etc) or every 12 weeks after the last dose of atezolizumab (if infusions are delayed), whichever is earlier. | | X | |
| Hematology and Chemistry by central lab (Section 5.6.5) | ≤ 14 days | C1D1[g,h] predose | Day 1 of every cycle or every three weeks after the last dose of atezolizumab (if infusions are delayed)[g,h], whichever is earlier. | | X | |
| Tumor markers: PSA (CRPC), CA125 (OC), AFP (HCC), and CEA (CRC), thyroglobulin (DTC) (Section 5.6.9.4) | ≤ 28 days | | PSA (CRPC), CA125 (OC), AFP (HCC), CEA (CRC), thyroglobulin (DTC): Day 1 of every 3rd cycle (or every 9 weeks, whichever is earlier) for first 12 months and Day 1 of every 5th cycle (or every 15 weeks, whichever is earlier) thereafter until the earlier of initiation of subsequent systemic anticancer therapy or permanent loss to radiographic follow-up (including hospice admission). | | | |
| Follicle stimulating hormone by central lab (Section 5.6.5) [a, i] | ≤ 28 days | | | | | |
| For CRPC only: testosterone (Section 5.6.5) [a] | ≤ 28 days | | | | | |
| Hepatitis screening[j] by central lab (Section 5.6.5) | X | | | | | |

## Appendix B: Schedule of Assessments for the Expansion Stage (Combination-Therapy Cohorts, Exploratory Single-Agent Cabozantinib [SAC] Cohorts, and Exploratory Single-Agent Atezolizumab [SAA] Cohort)

| | **Pre-enrollment** | **Post-enrollment** | | | | |
|---|---|---|---|---|---|---|
| **Assessment:** | **Screening[a] (Before First Dose)** | **Cycle 1 (± 3 days)** | **Cycles 2 through 8 (± 3 days)** | **Cycles 9 and Above (± 5 days)** | **30-Day Post-Treatment Follow-Up (+14 days)** | **Extended Follow Up** |
| PT/INR and PTT by central lab (Section 5.6.5) | ≤ 14 days | C1D1[f] predose | Day 1 of every 3rd cycle starting with C3D1 (ie, C3D1, C6D1, etc) or every nine weeks after the last dose of atezolizumab (if infusions are delayed), whichever is earlier. | | X | |
| Urinalysis by **local** lab (Section 5.6.5) | ≤ 14 days | C1D1[g] predose | Day 1 of every cycle or every three weeks after the last dose of atezolizumab (if infusions are delayed)[g], whichever is earlier. | | X | |
| Urine chemistry incl. UPCR by central lab (Section 5.6.5) | ≤ 14 days | C1D1[f] predose | Day 1 of every other cycle starting with C3D1 (ie, C3D1, C5D1, etc) or every six weeks after the last dose of atezolizumab (if infusions are delayed) , whichever is earlier. | | X | |
| Pregnancy test by **local** lab (Section 5.6.5) | ≤ 7 days (serum) | C1D1[f] predose (serum) | Day 1 of every cycle or every three weeks after the last dose of atezolizumab (if infusions are delayed) (serum or urine), whichever is earlier. | | | |
| Thyroid function test by central lab (Section 5.6.5) | ≤ 14 days | C1D1[f] predose | Day 1 of every 3rd cycle starting with C3D1 (ie, C3D1, C6D1, etc) or every nine weeks after the last dose of atezolizumab (if infusions are delayed), whichever is earlier. | | X | |
| Archival tumor tissue sample[k] (Section 5.6.8) | X | | | | | |
| Optional tumor biopsy (Section 5.6.8) | After the first dose of study treatment (6 weeks or later but prior to progressive disease) if archival tissue is evaluable. If archival samples are not evaluable, then tissue may be collected before the first dose of study treatment. If tumor biopsies are to be performed prior to first dose of study treatment, cabozantinib treatment will not be given until complete wound healing has occurred; if optional tumor biopsies are to be performed after first dose, cabozantinib treatment must be interrupted for at least 5 days before optional tumor biopsies are performed and may not be reinitiated until adequate wound healing has occurred. | | | | | |

## Appendix B: Schedule of Assessments for the Expansion Stage (Combination-Therapy Cohorts, Exploratory Single-Agent Cabozantinib [SAC] Cohorts, and Exploratory Single-Agent Atezolizumab [SAA] Cohort)

| | Pre-enrollment | Post-enrollment | | | | |
|---|---|---|---|---|---|---|
| **Assessment:** | **Screening[a] (Before First Dose)** | **Cycle 1 (± 3 days)** | **Cycles 2 through 8 (± 3 days)** | **Cycles 9 and Above (± 5 days)** | **30-Day Post-Treatment Follow-Up (+14 days)** | **Extended Follow Up** |
| Tumor assessment: CT/MRI **Chest, Abdomen, Pelvis, Neck** (Section 5.6.9) | ≤ 28 days | Unless otherwise described, CT of the chest, abdomen, and pelvis or CT of the chest with MRI of the abdomen and pelvis will be performed in all subjects at screening and every 6 weeks (± 5 days) after first dose (at W7D1, W13D1 etc). Upon completion of 12 months on study, these assessments will be performed every 12 weeks (± 7 days). For subjects with DTC and head & neck cancer, CT/MRI of the neck will be performed in addition to the CAP assessments. Subjects with head & neck cancer will be using the same imaging schedule after screening. For subjects with DTC the imaging frequency after screening will be every 9 weeks after initiation of study treatment throughout the first 12 months on study; upon completion of 12 months on study, these assessments will be performed every 12 weeks (± 7 days).<br>CT/MRIs are to be performed per the protocol-defined schedule regardless of whether study treatment is reduced, interrupted, delayed, or discontinued, and the tumor assessment schedule is independent of the atezolizumab dosing schedule. Tumor imaging will continue until radiographic disease progression per RECIST 1.1 as determined by the investigator. For subjects who discontinue study treatment before radiographic disease progression per RECIST 1.1, regularly scheduled imaging assessments should continue if possible until radiographic progression per RECIST 1.1 or initiation of subsequent anticancer therapy.<br>PR or CR per RECIST 1.1 at a given time point must be confirmed by repeat assessments ≥ 4 weeks after the criteria for response are first met. Subjects with PD per RECIST 1.1 who continue with study treatment are to have tumor measurement outcomes confirmed ≥ 4 weeks after the initial PD criteria were met. For subjects who continue treatment after the confirmatory tumor scans, regularly scheduled imaging will continue. | | | | |
| Tumor assessment: MRI/CT **Brain** (Section 5.6.9) | ≤ 28 days | MRI (or CT) of the brain will be performed at screening in all subjects with RCC, head and neck cancer (H&N), and NSCLC and for subjects with other tumor indications who have a history or clinical symptoms of brain metastasis. After first dose, MRI (or CT) scans of the brain are only required in subjects with documented, treated brain metastasis. Assessments will be performed every 12 weeks (± 7 days) after first dose (at W13D1, W26D1 etc). The schedule for these assessments is independent of the atezolizumab dosing schedule. To ensure image consistency, the same imaging modalities and acquisition protocols used at screening are to be used for subsequent tumor assessments. (Note: in order to meet the eligibility requirements of the study, brain metastasis must have been treated and stable for at least 4 weeks before first dose of study treatment. Subjects without documented brain metastasis during the screening assessment are not required to undergo brain imaging after starting treatment unless clinically indicated).<br>CT/MRIs are to be performed per the protocol-defined schedule regardless of whether study treatment is reduced, interrupted, delayed, or discontinued, and the tumor assessment schedule is independent of the atezolizumab dosing schedule. Tumor imaging will continue until radiographic disease progression per RECIST 1.1 as determined by the investigator. For subjects who discontinue study treatment before radiographic disease progression per RECIST 1.1, regularly scheduled imaging assessments should continue if possible until radiographic progression per RECIST 1.1 or initiation of subsequent anticancer therapy. | | | | |
| Bone scans (Section 5.6.9) | ≤ 28 days | Technetium bone scans (TBS) will be performed at screening in all subjects with CRPC and for subjects with other tumor indications who have a history or clinical symptoms (ie, bone pain) of bone metastases. After study treatment initiation bone scans are only required in subjects with documented bone lesions or if clinically indicated by signs and symptoms suggestive of new bone metastases. Assessments after the first dose will follow routine clinical practice (approximately every 12 weeks throughout the first 12 months and every 24 weeks thereafter). Bone scan findings alone cannot be used for the determination of progression or response in this study and need to be corroborated by CT/MRI. Bone lesions corroborated by CT/MRI must be reported as non-target or new lesions. PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. Bone scan evaluations will end on the date of last CT/MRI scan. If the bone scan schedule does not coincide with the last CT/MRI scan, no additional bone scan is needed after the last CT/MRI has been performed. | | | | |

## Appendix B: Schedule of Assessments for the Expansion Stage (Combination-Therapy Cohorts, Exploratory Single-Agent Cabozantinib [SAC] Cohorts, and Exploratory Single-Agent Atezolizumab [SAA] Cohort)

| | Pre-enrollment | Post-enrollment | | | | |
|---|---|---|---|---|---|---|
| **Assessment:** | **Screening[a] (Before First Dose)** | **Cycle 1 (± 3 days)** | **Cycles 2 through 8 (± 3 days)** | **Cycles 9 and Above (± 5 days)** | **30-Day Post-Treatment Follow-Up (+14 days)** | **Extended Follow Up** |
| **Pharmacokinetic and Biomarker Blood Sample Assessment for the *Standard Dosing Schedule*** | | | | | | |
| PK blood samples[l] (Section 5.6.6.1) | | C1D1 (Combination-Therapy Expansion Cohorts: before treatment, approximately 5 min after atezolizumab infusion & 2 h after cabozantinib dose; Exploratory SAC Cohorts: before treatment; Exploratory SAA Cohort: before treatment, approximately 5 min after atezolizumab infusion) and predose on C2D1 and C3D1. | | | | |
| Blood sample–Pharmacogenetic (Section 5.6.7) | | X predose | | | | |
| Blood sample–immune cell profiling by FACS[m] (Section 5.6.8) | | Predose on C1D1 and C2D1. (may be performed at selected sites) | | | | |
| Blood sample—Immunogenicity (Section 5.6.7) | | Predose on C1D1, C3D1, and C7D1 predose (for the Expansion Cohorts and SAA Cohort only) | | | X (for the Expansion Cohorts and SAA Cohort only) | |
| Blood sample–serum/plasma biomarker[m] (Section 5.6.8) | | Predose on C1D1, C2D1, and C3D1 An optional sample may be collected at the first sign of progression per the investigator. | | | | |
| Blood sample–cell and/or plasma pharmacogenomics [m] (Section 5.6.8) | | Predose on C1D1, C2D1, and C3D1 An optional sample may be collected at the first sign of progression per the investigator. | | | | |
| Concomitant medication (Section 7) | Document concomitant medication taken from 28 days before first dose of study treatment through 30 days after the date of the decision to discontinue study treatment | | | | | |
| Adverse events (Sections 8.1, 8.2, and 8.3.1) | Document new or worsening AEs from informed consent through 30 days (90 days for AESIs) after the date of the decision to permanently discontinue study treatment in source documents. AE information will be collected at study visits and may also be collected at any time over the phone or by spontaneous subject report. See the CRF Completion Guidelines for instructions on entering these data on Medical History and/or AE CRFs and Section 8.2 for SAE reporting requirements.<br><br>At the date of the first dose of study treatment, AEs will be documented pre- and post-dose. Certain AEs and all SAEs that are ongoing at the time of the Post-Treatment Follow-Up Visit 30 (+14) days after the date of the decision to permanently discontinue study treatment are to be followed until resolution or determination by the investigator that the event is stable or irreversible (see Section 8.4). | | | | | |

## Appendix B: Schedule of Assessments for the Expansion Stage (Combination-Therapy Cohorts, Exploratory Single-Agent Cabozantinib [SAC] Cohorts, and Exploratory Single-Agent Atezolizumab [SAA] Cohort)

| | Pre-enrollment | Post-enrollment | | | | |
|---|---|---|---|---|---|---|
| **Assessment:** | **Screening[a] (Before First Dose)** | **Cycle 1 (± 3 days)** | **Cycles 2 through 8 (± 3 days)** | **Cycles 9 and Above (± 5 days)** | **30-Day Post-Treatment Follow-Up (+14 days)** | **Extended Follow Up** |
| Atezolizumab dosing[n] (Not administered for Exploratory SAC Cohorts; Section 6.2) | | Atezolizumab will be administered by IV infusion at the clinic; first infusion on C1D1; Subsequent atezolizumab infusions will be administered every three weeks (-2 days) on Day 1 of each cycle until study treatment is discontinued. | | | | |
| Cabozantinib dosing (Not administered for Exploratory SAA Cohort; Section 6.2) | | Cabozantinib will administered in clinic C1D1 and then will be taken once daily at home until study treatment is discontinued | | | | |
| Dispense/return of oral study drug and compliance accounting[o] (Section 6.3) | | Cabozantinib is to be dispensed to subjects every 3 weeks | | | | |
| Additional anticancer treatment and survival status (Sections 5.3 and 5.6.11) | | | | | | Every 12 weeks (± 14 days) after 30-day post-treatment follow-up visit until death |

[a] Results of screening assessments must be reviewed before first dose of study treatment to confirm that the subject meets the eligibility criteria.

[b] Informed consent may be obtained greater than 28 days prior to first dose of study treatment, 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] Symptom-directed physical examination will be conducted on C1D1 before first dose of study treatment and at subsequent safety assessment visits.

[d] Vital signs should always be assessed within 60 min prior to initiation of atezolizumab infusions, and further vital sign assessment should be performed during and after the infusion as clinically indicated.

[e] Additional ECGs are to be performed if clinically indicated.

[f] This assessment is intended to confirm suitability for treatment after screening and prior to first dose. If this assessment has been performed during screening within 14 days (7 days for pregnancy test) prior to first dose (C1D1), this assessment does not need to be performed on C1D1 unless the subject's clinical status has changed (eg, onset of new symptoms indicative of clinical deterioration). If the assessment is performed on C1D1, the results must be available to and reviewed by the investigator prior to any treatment being administered.

[g] Serum chemistry, hematology, and urinalysis laboratory samples must be collected and the results must be reviewed within 72 h before any atezolizumab infusion administered on study.

[h] Local laboratory assessments for these panels may be obtained and used if the results are required by the investigator in a rapid timeframe. See Section 5.6.5 and the Laboratory Manual for more detailed information on laboratory assessments.

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

[j] For all tumor types except HCC, Hepatitis B surface antigen and Hepatitis C antibody (with reflex testing of HCV RNA if antibody test is positive) are to be assessed at screening. For HCC subjects, Hepatitis B surface antigen, Hepatitis B core antibody, Hepatitis B e-antigen/e-antibody, Hepatitis B DNA, Hepatitis D testing for Hepatitis B positive, Hepatitis C antibody, and Hepatitis C virus RNA are to be assessed at screening.

[k] Tumor tissue (archival) will be obtained prior to first dose of study treatment whenever available. Formalin-fixed paraffin embedded (FFPE) tumor blocks are preferred but in cases where this is not possible, tumor slides should be obtained. See Translational Medicine Laboratory Manual for specific instructions.

[l] Plasma samples will be collected for cabozantinib PK in the Combination-Therapy Expansion Cohorts and the Exploratory SAC Cohorts; Serum samples will be collected for atezolizumab PK in the Expansion Cohorts and the Exploratory SAA Cohort (not applicable to the Exploratory SAC Cohorts). Pre-dose PK samples for cabozantinib and atezolizumab for C1D1, C2D1, and C3D1 for the Combination-Therapy Expansion and Exploratory SAA Cohorts should be collected within 15 minutes before atezolizumab dose; it is acceptable to draw this sample up to 1 hour prior to atezolizumab dose. For the Exploratory SAC Cohorts, predose PK samples for cabozantinib should be collected prior to cabozantinib dose on C1D1; after C1D1, cabozantinib PK samples should be collected approximately 8 or more hours after the previous dose of cabozantinib, and if cabozantinib will be administered on that day, PK samples should be collected prior to cabozantinib administration. The investigator will ask the subject for the date and time of the most recent prior dose of cabozantinib, and this information will be recorded on the appropriate CRF page.

[m] An additional blood sample should be collected if an optional tumor tissue sample is obtained and such tissue sample collection does not coincide with scheduled blood collection for biomarker analysis.

[n] Atezolizumab doses are not to be administered less than 19 days apart.

[o] In exceptional circumstances (eg, COVID-19 pandemic), alternative methods of distribution of oral treatment to subjects may be considered in accordance with the study site's local policies and all applicable regulations.

## Appendix C: Second Agent Add-On Stage - Eligibility Criteria and Schedule of Assessments

For subjects in the SAC or SAA cohorts: at the time of documented Investigator-determined radiographic progression per RECIST 1.1, investigators may request subjects begin combination therapy and undergo study assessments as defined herein. To be eligible for combination therapy, subjects must not have met any of the criteria that require discontinuation of study treatment (see Section 3.8). Furthermore, investigators must establish subject eligibility according to the criteria provided in this appendix before receiving combination in this stage of study.

Subjects who are ineligible or opt not to receive combination therapy can continue on single-agent therapy if, in the opinion of the Investigator, they are experiencing clinical benefit and meet the criteria to receive treatment beyond radiographic progression outlined in Section 5.2. Study assessments for subjects from SAC and SAA cohorts who do not receive combination treatment in the Second Agent Add-On Stage are to continue as described in Appendix B.

Subjects without Investigator-assessed radiographic progression per RECIST 1.1 are not eligible for the Second Agent Add-On Stage and are to continue to receive study treatment and undergo study assessments according to the schedule in Appendix B.

Screening of SAC and SAA subjects to receive combination therapy in the Second Agent Add-On Stage may continue, as appropriate, until the transition of the study to the Maintenance Phase. Subjects in the SAC and SAA cohorts who experience Investigator-assessed radiographic progression per RECIST 1.1 on single-agent therapy during the Maintenance Phase will not be eligible to receive combination treatment on study.

Assessments for the Second Agent Add-On Stage are outlined in the table provided in this appendix. Special accommodations during the global COVID-19 pandemic are described in Appendix M.

**Eligibility Criteria for Receiving Combination Therapy Following SAC or SAA Treatment**

The numbering of the criteria is maintained from the start of the study (Section 4.2 Inclusion Criteria and Section 4.3 Exclusion Criteria). “Not applicable” rows below refer to eligibility criteria from the start of the study that are not relevant for the Second Agent Add-On Stage as these subjects have either already fulfilled the criteria upon study entry, or the criteria are not a requirement for the Second Agent Add-On Stage. Assessments that were performed for purposes

of subject monitoring during single-agent treatment within the defined screening window do not need to be repeated for the purpose of determining subject eligibility for the Second Agent Add-On Stage.

**Inclusion Criteria**

1. Not applicable
2. Imaging scans indicating radiographic disease progression on single-agent treatment as assessed by the Investigator per RECIST 1.1 ≤ 4 weeks before first dose of second agent on Second Agent Add-On Stage.
3. Not applicable
4. Recovery to baseline or ≤ Grade 1 CTCAE v4 from toxicities related to any prior treatments, unless AE(s) are clinically nonsignificant and/or stable on supportive therapy.
5. Not applicable
6. ECOG Performance Status of 0 or 1.
7. Adequate organ and marrow function, based upon meeting all of the following laboratory criteria within 14 days before first dose of the second agent of combination treatment in the Second Agent Add-On Stage:
    a. ANC ≥ 1500/μL (≥ 1.5 × $10^9$/L) without granulocyte colony-stimulating factor support within 2 weeks before screening laboratory sample collection.
    b. White blood cell count ≥ 2500/μL (≥ 2.5 × $10^9$/L).
    c. Platelets ≥ 100,000/μL (≥ 100 × $10^9$/L) without transfusion within 2 weeks before screening laboratory sample collection.
    d. Hemoglobin ≥ 9 g/dL (≥ 90 g/L) without transfusion within 2 weeks before screening laboratory sample collection.
    e. ALT, AST, and ALP ≤ 3 × ULN. ALP ≤ 5 × ULN with documented bone metastases. For subjects with mCRPC with documented bone metastases: ALT ≤ 3 × ULN, AST ≤ 3 × ULN, and ALP ≤ 10 × ULN. If ALP > 5 × ULN in mCRPC subjects, then it must be demonstrated that it is predominantly bone-specific ALP.
    f. Total bilirubin ≤ 1.5 × ULN (for subjects with Gilbert's disease ≤ 3 × ULN).
    g. Serum creatinine ≤ 1.5 × ULN or calculated creatinine clearance ≥ 40 mL/min (≥ 0.67 mL/sec) using the Cockcroft-Gault equation (see Table 5-2 for Cockcroft-Gault formula).
    h. UPCR ≤ 1 mg/mg (≤ 113.2 mg/mmol).
8. Not applicable
9. Not applicable
10. Not applicable

**Exclusion Criteria**

1. Not applicable
2. Not applicable
3. Not applicable
4. Not applicable
5. Not applicable
6. Radiation therapy for bone metastasis within 2 weeks, any other local radiation therapy within 4 weeks before first dose of the second agent of combination treatment in the Second Agent Add-On Stage. Subjects with clinically relevant ongoing complications from prior radiation therapy are not eligible.
7. Known brain metastases or cranial epidural disease unless adequately treated with radiotherapy and/or surgery (including radiosurgery) and stable for at least 4 weeks before first dose of the second agent of combination treatment in the Second Agent Add-On Stage. Eligible subjects must be neurologically asymptomatic and without corticosteroid treatment at the time of first dose of the second agent of combination treatment in the Second Agent Add-On Stage.
8. Concomitant anticoagulation with oral anticoagulants 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 specified direct factor Xa inhibitors rivaroxaban, edoxaban, or apixaban in subjects without known brain metastases who are on a stable dose of the anticoagulant for at least 1 week before first dose of the second agent of combination treatment and without clinically significant hemorrhagic complications from the anticoagulation regimen or the tumor.
9. Diagnosis of immunodeficiency or is receiving systemic steroid therapy (> 10 mg daily prednisone equivalent) or any other form of immunosuppressive therapy within 2 weeks prior to first dose of the second agent of combination treatment in the Second Agent Add-On Stage. Inhaled, intranasal, intraarticular, and topical corticosteroids and mineralocorticoids are allowed.
   *Note: Adrenal replacement steroid doses > 10 mg daily prednisone equivalent are permitted in the absence of active autoimmune disease. Transient short-term use of systemic corticosteroids for allergic conditions (eg, contrast allergy) is also allowed.*
10. Not applicable

11. The subject has uncontrolled, significant intercurrent or recent illness including, but not limited to, the following conditions:
    1. For the SAA Cohort (ie, subjects to initiate cabozantinib treatment in the Second Agent Add-On Stage)
        a. Cardiovascular disorders:
            i. Congestive heart failure New York Heart Association Class 3 or 4, unstable angina pectoris, serious cardiac arrhythmias.
            ii. Uncontrolled hypertension defined as sustained blood pressure (BP) > 140 mm Hg systolic or > 90 mm Hg diastolic despite optimal antihypertensive treatment.
            iii. Stroke (including TIA), MI, or other ischemic event, within 6 months before first dose of the second agent of combination treatment in the Second Agent Add-On Stage. Subjects with a diagnosis of PE or DVT within 6 months are allowed if stable, asymptomatic, and treated with anticoagulation for at least 1 week before first dose of the second agent of combination treatment in the Second Agent Add-On Stage.
        b. Gastrointestinal (GI) disorders including those associated with a high risk of perforation or fistula formation:
            i. Tumors invading the GI-tract, active peptic ulcer disease, inflammatory bowel disease, diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis, or acute obstruction of the pancreatic or biliary duct, gastric outlet, or bowel.
            ii. Abdominal fistula, GI perforation, or intra-abdominal abscess within 6 months before first dose of the second agent of combination treatment in the Second Agent Add-On Stage. Note: Complete healing of an intra-abdominal abscess must be confirmed before first dose of the second agent of combination treatment in the Second Agent Add-On Stage.
            iii. Gastric or esophageal varices that are untreated or incompletely treated with bleeding or high risk for bleeding.
        c. Clinically significant hematuria, hematemesis, or hemoptysis of > 0.5 teaspoon (2.5 mL) of red blood, or other history of significant bleeding (eg, pulmonary hemorrhage) within 12 weeks before first dose of the second agent of combination treatment in the Second Agent Add-On Stage.
        d. Cavitating pulmonary lesion(s) or known endobronchial disease manifestation.
        e. Lesion invading a major blood vessel including, but not limited to, inferior vena cava, pulmonary artery, or aorta.
        f. Other clinically significant disorders such as:

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

ii. Free thyroxine (FT4) outside the laboratory normal reference range. Asymptomatic subjects with FT4 abnormalities can be eligible after sponsor approval.

iii. Known history of COVID-19 unless the subject has demonstrated recovery from the disease prior to receiving study treatment in the Second Agent Add-On Stage.

2. For the SAC Cohorts (ie, subjects to initiate atezolizumab treatment in the Second Agent Add-On Stage)

   a. Cardiovascular disorders:

      i. Congestive heart failure New York Heart Association Class 3 or 4, unstable angina pectoris, serious cardiac arrhythmias.

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

      iii. Stroke (including TIA), MI, or other ischemic event, within 6 months before first dose of the second agent of combination treatment in the Second Agent Add-On Stage. Subjects with a diagnosis of PE or DVT within 6 months are allowed if stable, asymptomatic, and treated with anticoagulation for at least 1 week before first dose of the second agent of combination treatment in the Second Agent Add-On Stage.

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

      i. Active peptic ulcer disease, inflammatory bowel disease, diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis, or acute obstruction of the pancreatic or biliary duct, gastric outlet, or bowel.

   c. Lesion invading a major blood vessel including, but not limited to, inferior vena cava, pulmonary artery, or aorta.

   d. Other clinically significant disorders such as:

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

         - A history of autoimmune-related hypothyroidism and on thyroid replacement hormone therapy

           *Note: Subjects with prior history of thyroiditis are allowed if they have undergone sub-total, near-total, or total thyroidectomy.*

- Controlled Type 1 diabetes mellitus and on an insulin regimen
- Asthma
- Eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only provided all of following are true:
  - Rash covers < 10% of body surface area
  - Disease is well controlled at baseline and requires only low-potency topical corticosteroids
  - No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high potency or oral corticosteroids within the previous 12 months

ii. Active infection requiring systemic treatment, infection with known HIV or AIDS-related illness, acute or chronic hepatitis B or C infection, or a known positive test for tuberculosis infection if supported by clinical or radiographic evidence of disease. Subjects with history of COVID-19 must have recovered from the disease prior to receiving study treatment in the Second Agent Add-On Stage.

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

iv. Free thyroxine (FT4) outside the laboratory normal reference range. Asymptomatic subjects with FT4 abnormalities can be eligible after sponsor approval.

12. Major surgery (eg, GI surgery, removal or biopsy of brain metastasis) within 4 weeks or minor surgery (eg, simple excision, tooth extraction) within 10 days before first dose of the second agent of combination treatment. Complete wound healing from surgery must have occurred before first dose of the second agent. Subjects with clinically relevant ongoing complications from prior surgery are not eligible.
13. QTcF > 500 ms per ECG within 14 days before first dose of the second agent of combination treatment in the Second Agent Add-On Stage (see Section 5.6.4 for Fridericia formula).

    *Note: If a single ECG shows a QTcF with an absolute value > 500 ms, two additional ECGs at intervals of approximately 3 min must be performed within 30 min after the initial ECG, and the average of these three consecutive results for QTcF will be used to determine eligibility (ie, if the average is ≤ 500 ms the subject is eligible).*
14. Not applicable
15. Inability to swallow tablets.
16. Not applicable
17. Not applicable

**Schedule of Assessments for Second Agent Add-On Stage:**

The schedule of required assessments presented in the appendix table below is to be followed for subjects who received combination treatment of cabozantinib and atezolizumab after radiographically progressing on single-agent treatment in an SAC or SAA Cohort.

Most study assessments and procedures (including treatment administration) will be performed in cycles. Second Agent Cycle 1 Day 1 (aoC1D1) is defined as the date of first dose of the new study treatment (ie, for subjects enrolled in an SAC Cohort, aoC1D1 of the Second Agent Add-On Stage will be defined as the date they receive the first dose of atezolizumab; for subjects enrolled in SAA Cohort, aoC1D1 of the Second Agent Add-On Stage will be defined as the date they receive the first dose of cabozantinib). For subjects in the SAA Cohort who transition to combination treatment in the Second Agent Add-On Stage, the first dose of cabozantinib treatment (ie, aoC1D1) must occur on an atezolizumab dosing day.

Cycles for the Second Agent Add-On Stage: Cycles may extend beyond 21 days if atezolizumab dosing is delayed. A cycle is generally the 21-day interval starting with the date of an atezolizumab infusion and ending with the day before the next atezolizumab infusion. However, if atezolizumab treatment is discontinued but cabozantinib treatment is allowed to continue with the notification of the Sponsor, each consecutive 21-day interval starting with the date of the decision to discontinue atezolizumab will be defined as a cycle. If the decision to discontinue atezolizumab occurs less than 21 days after the last infusion, then the next cycle will begin on the 22$^{nd}$ day after the last infusion. The date of the decision to discontinue study treatment is defined for each subject as the later of (a) the date of the decision of the investigator to permanently discontinue study treatment or (b) the date of the last dose of study treatment taken by the subject.

During an atezolizumab dose delay, subjects should return to the site for scheduled safety visits every three weeks from the last dose of atezolizumab. Further, the study site should perform unscheduled visits or telephone calls weekly (or more frequently) as clinically indicated to monitor subject safety and appropriateness for re-treatment with study treatment. Other unscheduled visits are permitted whenever necessary. See Section 5.5 for further details.

Imaging assessments (CT, MRI, bone scan) are to be performed at protocol-defined, fixed intervals based on the first dose of study treatment (defined as Add-On Week 1 Day 1 [aoW1D1]); all subsequent time points for these assessments will apply the same nomenclature,

the timing of which will not be modified as a result of modifications or discontinuations of treatment administration.

Unless otherwise indicated, in the absence of side effects all scheduled visits will occur within windows for the protocol-specified visit schedule. If the subject experiences side effects, study treatment can be modified or delayed as described in Section 6.5. If the subject is unable to have a study assessment taken within the defined time window due to an event outside of his or her control (eg, clinic closure, personal emergency, inclement weather, vacation), the assessment should be performed as close as possible to the required schedule. Special accommodations during the global COVID-19 pandemic are described in Appendix M. Laboratory panels for serum chemistry, hematology, and urinalysis are defined in Section 5.6.5.

## Appendix C: Schedule of Assessments for the Second Agent Add-On Stage: Exploratory Single-Agent Cabozantinib [SAC] Cohorts and Exploratory Single-Agent Atezolizumab [SAA] Cohort

| Assessment: | Screening before Starting 2nd Agent[a] | Cycle 1 (± 3 days) | Cycles 2 through 8 (± 3 days) | Cycles 9 and Above (± 5 days) | 30-Day Post-Treatment Follow-Up (+14 days) | Extended Follow Up |
|---|---|---|---|---|---|---|
| Informed consent (Section 5.1) | X[b] | | | | | |
| Physical examination[c] + weight (Section 5.6.2) | ≤ 14 days | aoC1D1 predose | Day 1 of every cycle or every three weeks after the last dose of atezolizumab (if infusions are delayed), whichever is earlier. | | X | |
| ECOG Performance status (Section 5.6.2, Appendix F) | ≤ 14 days | aoC1D1 predose | Day 1 of every cycle or every three weeks after the last dose of atezolizumab (if infusions are delayed), whichever is earlier. | | X | |
| Vital signs (Section 5.6.3) | ≤ 14 days | aoC1D1[d] predose | Day 1 of every cycle or every three weeks after the last dose of atezolizumab (if infusions are delayed)[d], whichever is earlier. | | X | |
| 12-lead ECG (Section 5.6.4)[e] | ≤ 14 days | aoC1D1[f] predose | Day 1 of every 4th cycle starting with aoC3D1 (ie, aoC3D1, aoC7D1, etc) or every 12 weeks after the last dose of atezolizumab (if infusions are delayed), whichever is earlier. | | X | |
| Hematology and Chemistry (Section 5.6.5) | ≤ 14 days | aoC1D1[g,h] predose | Day 1 of every cycle or every three weeks after the last dose of atezolizumab (if infusions are delayed)[g,h], whichever is earlier. | | X | |
| Tumor markers: PSA (CRPC) (Section 5.6.9.4) | ≤ 14 days | | Day 1 of every 3rd cycle (or every 9 weeks, whichever is earlier) for first 12 months and Day 1 of every 5th cycle (or every 15 weeks, whichever is earlier) thereafter until the earlier of initiation of subsequent systemic anticancer therapy or permanent loss to radiographic follow-up (including hospice admission). | | | |
| For CRPC only: testosterone (Section 5.6.5)[a] | ≤ 14 days | | | | | |
| PT/INR and PTT (Section 5.6.5) | ≤ 14 days | aoC1D1[f] predose | Day 1 of every 3rd cycle starting with aoC3D1 (ie, aoC3D1, aoC6D1, etc) or every nine weeks after the last dose of atezolizumab (if infusions are delayed), whichever is earlier. | | X | |
| Urinalysis (Section 5.6.5) | ≤ 14 days | aoC1D1[g] predose | Day 1 of every cycle or every three weeks after the last dose of atezolizumab (if infusions are delayed)[g], whichever is earlier. | | X | |
| Urine chemistry incl. UPCR (Section 5.6.5) | ≤ 14 days | aoC1D1[f] predose | Day 1 of every other cycle starting with aoC3D1 (ie, aoC3D1, aoC5D1, etc) or every six weeks after the last dose of atezolizumab (if infusions are delayed) , whichever is earlier. | | X | |
| Pregnancy test (Section 5.6.5) | ≤ 14 days (serum) | aoC1D1[f] predose (serum) | Day 1 of every cycle or every three weeks after the last dose of atezolizumab (if infusions are delayed) (serum or urine), whichever is earlier. | | | |
| Thyroid function test (Section 5.6.5) | ≤ 14 days | aoC1D1[f] predose | Day 1 of every 3rd cycle starting with aoC3D1 (ie, aoC3D1, aoC6D1, etc) or every nine weeks after the last dose of atezolizumab (if infusions are delayed), whichever is earlier. | | X | |

## Appendix C: Schedule of Assessments for the Second Agent Add-On Stage: Exploratory Single-Agent Cabozantinib [SAC] Cohorts and Exploratory Single-Agent Atezolizumab [SAA] Cohort

| Assessment: | Screening before Starting 2nd Agent[a] | Cycle 1 (± 3 days) | Cycles 2 through 8 (± 3 days) | Cycles 9 and Above (± 5 days) | 30-Day Post-Treatment Follow-Up (+14 days) | Extended Follow Up |
|---|---|---|---|---|---|---|
| Optional tumor biopsy (Section 5.6.8) | After the first dose of the second agent of study treatment (6 weeks or later) if archival tissue is evaluable. If archival samples are not evaluable, then tissue may be collected before the first dose of second agent of study treatment.<br>If tumor biopsies are to be performed prior to first dose of the second agent of combination treatment, cabozantinib treatment will not be given until complete wound healing has occurred; if optional tumor biopsies are to be performed after first dose of the second agent of combination treatment, cabozantinib treatment must be interrupted for at least 5 days before optional tumor biopsies are performed and may not be reinitiated until adequate wound healing has occurred. | | | | | |
| Tumor assessment: CT/MRI **Chest, Abdomen, Pelvis, Neck** (Section 5.6.9) | Establish baseline based upon the most recent set of scans performed prior to starting 2nd agent; if these scans are > 4 weeks prior to first dose of second agent, new scans are required to establish baseline | Unless otherwise described, CT of the chest, abdomen, and pelvis or CT of the chest with MRI of the abdomen and pelvis will be performed in all subjects at screening and every 6 weeks (± 5 days) after first dose (at aoW7D1, aoW13D1 etc). Upon completion of 12 months on study, these assessments will be performed every 12 weeks (± 7 days). For subjects with DTC and head & neck cancer, CT/MRI of the neck will be performed in addition to the CAP assessments. CT/MRIs are to be performed per the protocol-defined schedule regardless of whether study treatment is reduced, interrupted, delayed, or discontinued, and the tumor assessment schedule is independent of the atezolizumab dosing schedule. Tumor imaging will continue until radiographic disease progression per RECIST 1.1 as determined by the investigator. For subjects who discontinue study treatment before radiographic disease progression per RECIST 1.1, regularly scheduled imaging assessments should continue if possible until radiographic progression per RECIST 1.1 or initiation of subsequent anticancer therapy.<br>PR or CR per RECIST 1.1 at a given time point must be confirmed by repeat assessments ≥ 4 weeks after the criteria for response are first met. Subjects with PD per RECIST 1.1 who continue with study treatment are to have tumor measurement outcomes confirmed ≥ 4 weeks after the initial PD criteria were met. For subjects who continue treatment after the confirmatory tumor scans, regularly scheduled imaging will continue. | | | | |
| Tumor assessment: MRI/CT **Brain** (Section 5.6.9) | Establish baseline based upon the most recent set of scans performed prior to starting 2nd agent; if these scans are > 4 weeks prior to first dose of second agent, new scans are required to establish baseline | MRI (or CT) of the brain will be performed at screening in all subjects with NSCLC and for subjects with other tumor indications who have a history or clinical symptoms of brain metastasis. After first dose, MRI (or CT) scans of the brain are only required in subjects with documented, treated brain metastasis. Assessments will be performed every 12 weeks (± 7 days) after first dose (at aoW13D1, aoW26D1 etc). The schedule for these assessments is independent of the atezolizumab dosing schedule. To ensure image consistency, the same imaging modalities and acquisition protocols used at screening are to be used for subsequent tumor assessments. (Note: in order to meet the eligibility requirements of the study, brain metastasis must have been treated and stable for at least 4 weeks before first dose of study treatment. Subjects without documented brain metastasis during the screening assessment are not required to undergo brain imaging after starting treatment unless clinically indicated).<br>CT/MRIs are to be performed per the protocol-defined schedule regardless of whether study treatment is reduced, interrupted, delayed, or discontinued, and the tumor assessment schedule is independent of the atezolizumab dosing schedule. Tumor imaging will continue until radiographic disease progression per RECIST 1.1 as determined by the investigator. For subjects who discontinue study treatment before radiographic disease progression per RECIST 1.1, regularly scheduled imaging assessments should continue if possible until radiographic progression per RECIST 1.1 or initiation of subsequent anticancer therapy. | | | | |

## Appendix C: Schedule of Assessments for the Second Agent Add-On Stage: Exploratory Single-Agent Cabozantinib [SAC] Cohorts and Exploratory Single-Agent Atezolizumab [SAA] Cohort

| Assessment: | Screening before Starting 2nd Agent[a] | Cycle 1 (± 3 days) | Cycles 2 through 8 (± 3 days) | Cycles 9 and Above (± 5 days) | 30-Day Post-Treatment Follow-Up (+14 days) | Extended Follow Up |
|---|---|---|---|---|---|---|
| Bone scans (Section 5.6.9) | Establish baseline based upon the most recent set of scans performed prior to starting 2nd agent; if these scans are > 4 weeks prior to first dose of second agent, new scans are required to establish baseline | Technetium bone scans (TBS) will be performed at screening in all subjects with CRPC and for subjects with other tumor indications who have a history or clinical symptoms (ie, bone pain) of bone metastases. After study treatment initiation bone scans are only required in subjects with documented bone lesions or if clinically indicated by signs and symptoms suggestive of new bone metastases. Assessments after the first dose will follow routine clinical practice (approximately every 12 weeks throughout the first 12 months and every 24 weeks thereafter). Bone scan findings alone cannot be used for the determination of progression or response in this study and need to be corroborated by CT/MRI. Bone lesions corroborated by CT/MRI must be reported as non-target or new lesions. PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. Bone scan evaluations will end on the date of last CT/MRI scan. If the bone scan schedule does not coincide with the last CT/MRI scan, no additional bone scan is needed after the last CT/MRI has been performed. | | | | |
| Blood sample—Immunogenicity (Section 5.6.7) | | SAC Cohorts: Predose on aoC1D1, aoC3D1, and aoC7D1<br>SAA Cohort: No samples required prior to 30-day follow-up visit | | | X | |
| Blood sample–cell and/or plasma pharmacogenomics[j] (Section 5.6.8) | | Predose on aoC1D1, aoC2D1, and aoC3D1<br>An optional sample may be collected at the first sign of progression per the investigator. | | | | |
| Concomitant medication (Section 7) | Document concomitant medication taken from 28 days before first dose of study treatment through 30 days after the date of the decision to discontinue study treatment | | | | | |
| Adverse events (Sections 8.1, 8.2, and 8.3.1) | Document new or worsening AEs from informed consent through 30 days (90 days for AESIs) after the date of the decision to permanently discontinue study treatment in source documents. AE information will be collected at study visits and may also be collected at any time over the phone or by spontaneous subject report. See the CRF Completion Guidelines for instructions on entering these data on AE CRFs and Section 8.2 for SAE reporting requirements.<br><br>Certain AEs and all SAEs that are ongoing at the time of the Post-Treatment Follow-Up Visit 30 (+14) days after the date of the decision to permanently discontinue study treatment are to be followed until resolution or determination by the investigator that the event is stable or irreversible (see Section 8.4). | | | | | |
| Atezolizumab dosing[i] Section 6.2) | | Atezolizumab will be administered by IV infusion at the clinic; first infusion on aoC1D1 if atezolizumab is the subject's second agent (ie, transition from SAC Cohort); Subsequent atezolizumab infusions will be administered every three weeks (-2 days) on Day 1 of each cycle until study treatment is discontinued. | | | | |
| Cabozantinib dosing Section 6.2) | | Cabozantinib will administered in clinic on aoC1D1 if the cabozantinib is the subject's second agent (ie, transition from SAA Cohort); otherwise cabozantinib will be taken once daily at home until study treatment is discontinued | | | | |
| Dispense/return of oral study drug and compliance accounting[k] (Section 6.3) | | Cabozantinib is to be dispensed to subjects every 3 weeks | | | | |

## Appendix C: Schedule of Assessments for the Second Agent Add-On Stage: Exploratory Single-Agent Cabozantinib [SAC] Cohorts and Exploratory Single-Agent Atezolizumab [SAA] Cohort

| Assessment: | Screening before Starting 2nd Agent[a] | Cycle 1 (± 3 days) | Cycles 2 through 8 (± 3 days) | Cycles 9 and Above (± 5 days) | 30-Day Post-Treatment Follow-Up (+14 days) | Extended Follow Up |
|---|---|---|---|---|---|---|
| Additional anticancer treatment and survival status (Sections 5.3 and 5.6.11) | | | | | | Every 12 weeks (± 14 days) after 30-day post-treatment follow-up visit until death |

[a] Results of screening assessments must be reviewed before first dose of study treatment to confirm that the subject meets the eligibility criteria. Assessments that were performed for purposes of subject monitoring during single-agent treatment within the defined screening window do not need to be repeated for the purpose of determining subject eligibility for the Second Agent Add-On Stage.

[b] Informed consent to participate in the Second Agent Add-On Stage must be collected after radiographic progression on single-agent treatment but may be obtained greater than 28 days prior to first dose of the second agent of study treatment.

[c] Symptom-directed physical examination will be conducted on aoC1D1 before first dose of study treatment and at subsequent safety assessment visits.

[d] Vital signs should always be assessed within 60 min prior to initiation of atezolizumab infusions, and further vital sign assessment should be performed during and after the infusion as clinically indicated.

[e] Additional ECGs are to be performed if clinically indicated.

[f] This assessment is intended to confirm suitability for treatment after screening and prior to first dose of second agent of combination treatment. If this assessment has been performed within 14 days prior to first dose (aoC1D1), this assessment does not need to be performed on aoC1D1 unless the subject's clinical status has changed (eg, onset of new symptoms indicative of clinical deterioration). If the assessment is performed on aoC1D1, the results must be available to and reviewed by the investigator prior to any treatment being administered.

[g] Serum chemistry, hematology, and urinalysis laboratory samples must be collected, and the results must be reviewed within 72 h before any atezolizumab infusion administered on study.

[h] Local laboratory assessments for these panels may be obtained and used if the results are required by the investigator in a rapid timeframe. See Section 5.6.5 and the Laboratory Manual for more detailed information on laboratory assessments.

[i] Atezolizumab doses are not to be administered less than 19 days apart.

[j] An additional blood sample should be collected if an optional tumor tissue sample is obtained and such tissue sample collection does not coincide with scheduled blood collection for biomarker analysis.

[k] In exceptional circumstances (eg, COVID-19 pandemic), alternative methods of distribution of oral treatment to subjects may be considered in accordance with the study site's local policies and all applicable regulations.

## Appendix D: Maintenance Phase

The purpose of the Maintenance Phase is to continue to provide long-term access to study drug(s) to subjects who are deriving clinical benefit even after evaluation of the study objectives has been completed. When sufficient data have been collected to adequately evaluate all study endpoints, and upon site notification by the Sponsor, subjects remaining on study treatment or who have not completed the Post-Treatment Follow-Up Visit will enter the study Maintenance Phase. Upon initiation of the Maintenance Phase, the Sponsor considers the safety and efficacy profile of the drug within this study to have been sufficiently established for regulatory purposes.

In the Maintenance Phase subjects who remain on treatment will continue to receive study treatment until a criterion for protocol-defined discontinuation has been met (protocol Section 3.8). Subjects are to undergo periodic safety assessments (including local laboratory tests) and tumor assessments; the nature and frequency of these assessments are to be performed per standard of care if allowed per local regulations. It is the Investigator's responsibility to ensure that subject visits occur frequently enough and adequate assessments are performed to ensure subject safety.

Subjects who enter the Maintenance Phase after discontinuing study treatment, but prior to their Post-Treatment Follow Up Visit, are to be followed in the Maintenance Phase until their Post-Treatment Follow Up Visit.

In order to continue to collect important safety information on subjects still enrolled in the study, reporting of SAEs, AESIs, and other reportable events (pregnancy and medication errors with sequelae) is to continue per protocol (Section 8.2.1).

Further, the following AEs, 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 (including irAEs), whether serious or not, leading to study treatment discontinuation
- Adverse Events (including irAEs), 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 6.4.

See Maintenance Phase Schedule of Assessments below. To receive study treatment supplies it may be necessary for subjects to visit the study site more frequently than clinic visits for safety and tumor evaluations performed per standard of care.

Site monitoring visits will occur at a reduced frequency to ensure adherence to GCP, protocol compliance, adequate subject safety follow-up, study drug accountability, and reporting of SAEs and other reportable events.

During the Maintenance Phase no data are to be entered into CRFs. Study central laboratory samples are not to be obtained. 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.

**Schedule of Assessments for the Maintenance Phase**

| Assessment | Study Period / Visit | |
|---|---|---|
| | **While Subject is Receiving Study Treatment (Until Treatment is Permanently Discontinued)** | **Post-Treatment Follow-Up Visit** |
| Study drug accountability | Every time study drug is dispensed | ✓[a] |
| Study treatment | Atezolizumab: Once every 3 weeks (-2 days); Cabozantinib: Daily<br>Study treatment may continue until a criterion for discontinuation is met (Section 3.6). Subjects in combination treatment cohorts may be allowed to discontinue treatment with one component of the combination and continue on the other with the notification of the Sponsor. | |
| Safety evaluation: *Clinical examination and local laboratory assessments per SOC* | Frequency per standard of care | |
| Reporting of SAEs, AESIs, and other reportable events (pregnancy and medication errors with sequelae) | Submit reports to Sponsor per Section 8.2 | |
| Reporting of AEs (including irAEs), serious or not:<br>• leading to study treatment discontinuation<br>• leading to study treatment dose modification (ie, causing study treatment to be interrupted, delayed, or reduced) | Submit reports to Sponsor per the same process as for reporting SAEs per Section 8.2<br><br>SAE reporting timeline requirements do not apply to non-serious events reported in these categories | |
| Tumor assessments: *Imaging methods per SOC* | Frequency per standard of care | |

AE, adverse event; irAE, immune-related adverse event; SAE, serious adverse event; SOC, standard of care.
No data will be entered into electronic case report forms. Do not submit local laboratory results to the study local laboratory management vendor.
[a] A post-treatment visit may be required for the purpose of returning all unused study medication still in the subject's possession.

## Appendix E: 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
- Subjects with transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent (eg, acute Lyme arthritis)

Contact the Sponsor regarding any uncertainty over autoimmune exclusions.

**Autoimmune Diseases and Immune Deficiencies**

| | | |
|---|---|---|
| Acute disseminated encephalomyelitis | Dermatomyositis | Neuromyotonia |
| Addison disease | Diabetes mellitus type 1 | Opsoclonus myoclonus syndrome |
| Ankylosing spondylitis | Dysautonomia | Optic neuritis |
| Antiphospholipid antibody syndrome | Epidermolysis bullosa acquisita | Ord thyroiditis |
| Aplastic anemia | Gestational pemphigoid | Pemphigus |
| Autoimmune hemolytic anemia | Giant cell arteritis | Pernicious anemia |
| Autoimmune hepatitis | Goodpasture syndrome | Polyarteritis nodosa |
| Autoimmune hypoparathyroidism | Graves disease | Polyarthritis |
| Autoimmune hypophysitis | Guillain-Barré syndrome | Polyglandular autoimmune syndrome |
| Autoimmune myocarditis | Hashimoto disease | Primary biliary cirrhosis |
| Autoimmune oophoritis | 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 disease | Mooren ulcer | Ulcerative colitis |
| | Morphea | Vitiligo |
| | Multiple sclerosis | Vogt-Koyanagi-Harada disease |
| | Myasthenia gravis | Wegener granulomatosis |

## Appendix F: Performance Status Criteria

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

## Appendix G: 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 receiving study treatment. Baseline assessments must be performed within the period defined in the protocol eligibility criteria.

Measurable lesions: Except for lymph nodes as described below, measurable lesions are defined as those that can be accurately measured in at least 1 dimension (longest diameter to be recorded) as ≥ 10 mm with CT scan (if CT scans have slice thickness greater than 5 mm the minimum size for a measurable lesion is twice the slice thickness).

- To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and recorded.
- MRI may be substituted for contrast-enhanced CT for lesions at some anatomical sites, but not for lesions in the lungs. The minimum size for measurability is the same as for CT (10 mm) as long as the scans are performed with slice thickness of 5 mm and no gap. If MRI is performed with thicker slices, the size of a measurable lesion at baseline should be twice the slice thickness. In the event there are interslice gaps, this also needs to be considered in determining the size of measurable lesions at baseline.

Nonmeasurable lesions: All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥10 to < 15 mm short axis), are considered nonmeasurable. Lymph nodes that have a short axis < 10 mm are considered nonpathological and are not be recorded or followed. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/ pulmonitis, and abdominal masses (not followed by CT or MRI), are considered as nonmeasurable.

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

which 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 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 < 10 mm are considered non-pathological and are not to be recorded or followed.

To be considered progression of non-target lesions in the presence of measurable disease, unequivocal progression is defined as substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of the therapy.

**Special Consideration**

*Lesions by clinical examination* will not be used for response in this study.

*Cystic lesions*

- Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same subject, these are preferred for selection as target lesions.

*Bone lesions*

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the *soft tissue component* meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

*Lesions with prior local treatment*

- Lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are not considered measurable.

**Imaging Methods**

The same method of assessment and the same technique used to characterize each identified and reported lesions at baseline should be used during each follow-up assessment. All measurements should be taken and recorded in metric notation using a ruler or calipers. Imaging based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but assessed by clinical examination (referring to biopsy-proven visible lesion(s) on the chest).

Chest x-ray: Chest x-ray will not be used for response assessment in this study.

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

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

Low dose non-contrast CT images from combined positron emission tomography/computed tomography (PET/CT) imaging cannot be used for tumor evaluations in this study.

Ultrasound: Ultrasound will not be used for response assessment in this study.

Bone scans will be used to assess the presence or disappearance of the bone component of bone lesions. CT or MRI scan will be used to confirm results of bone scans. Preferred method for confirmation is MRI.

Bone scan findings alone cannot be used for the determination of progression or response in this study and need to be corroborated by CT/MRI. Bone lesions corroborated by CT/MRI must be reported as non-target or new lesions. PET scan or plain films are not considered adequate imaging techniques to measure 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 post-baseline (follow-up) evaluations the baseline classification (target, nontarget) is to be maintained and lesions are to be documented and described in a consistent fashion over time (eg, recorded in the same order on source documents).

At each assessment, a sum of the diameters (longest for nonnodal lesions, short axis for nodal lesions) for all target lesions will be calculated and included in source documents. The *baseline sum of the diameters* (SoD) will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease. The lowest SoD (nadir) since (and including) the baseline value will be used as reference for evaluating progression.

After baseline, target lesions should have the actual size documented, if possible, even if the lesions become very small. If in the opinion of the radiologist the lesion has likely disappeared, 0

mm should be recorded. If the lesion is present but too small to measure, an indicator for ‘too small to measure’ should be included in source documents.

For target lesions, measurements should be taken and recorded in metric notation.

Nontarget lesions are to be assessed qualitatively (present, resolved, or unequivocal progression) and new lesions, if any, are to be documented separately.

At each evaluation, progression status is to be determined based upon the time point status for target lesions, nontarget lesions, and new lesions.

Finding of new lesions should not be attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor. Necrosis of pre-existing lesions as part of a response to treatment should be excluded before defining a ‘new’ cystic lesion. A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion. If a new lesion is equivocal because of its small size, repeat scans need to confirm there is definitely a new lesion, and progression should be declared using the date of the initial scan.

Time point progression cannot be based solely on bone scan findings. Bone scans are to be used to direct corroborative imaging with CT/MRI if necessary. These CT/MRI findings will be used for the determination of progression.

## TIME POINT RESPONSE CRITERIA

| Target Lesion Time Point Response (TPR) | |
|---|---|
| **Complete Response (CR)** | Disappearance of all target lesions. All pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm. |
| **Partial Response (PR)** | At least a 30% decrease in SoD of target lesions, taking as a reference the baseline SoD. |
| **Stable Disease (SD)** | Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. |
| **Progressive Disease (PD)** | At least a 20% increase in the SoD of target lesions, taking as a reference the smallest (nadir) SoD since (and including) baseline. In addition to the relative increase of 20%, the SoD must also demonstrate an absolute increase of at least 5 mm. |
| **Not Applicable (NA)** | No target lesion identified at baseline. |
| **Unable to Evaluate (UE)** | One or more target lesions are not imaged and the remainder of the SoD compared with the nadir SoD does not meet the criterion for PD. |

SoD, baseline sum of diameters (longest for non-nodal lesions; short axis for nodal lesions).

If the target lesion for a subject meet the criteria for both PR and PD at a given time point, the target lesion response is PD.

If the nadir of SoD is 0 (ie, the subject had a prior target lesion CR), the reappearance of any prior target lesion to any degree constitutes PD.

| Non-Target Lesion Time Point Response (TPR) | |
|---|---|
| **Complete Response (CR)** | Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm short axis). |
| **Non-CR / Non-PD** | Persistence of one or more non-target lesion(s). |
| **Progressive Disease (PD)** | Unequivocal progression of non-target lesions. Unequivocal progression should normally not trump target lesion status. It must be representative of overall disease status change, not a single lesion increase. |
| **Not Applicable (NA)** | No non-target lesions identified at screening. |
| **Unable to Evaluate (UE)** | One or more non-target lesions are not imaged and the remaining non-target lesions do not meet the criterion for PD. |

| New Lesion Time Point Response (TPR) | |
|---|---|
| **Yes** | Lesion present at follow-up visit either for the very first time or re-appearing (ie, lesion was present at baseline, disappeared at a follow-up visit and re-appeared later). Note: The appearance of one or more new lesions on CT or MRI scan is considered progression if these findings are unequivocally not due to a change in the imaging technique or modality. On bone scan, new lesions are not sufficient to qualify as PD. Confirmation should be obtained by performing CT or MRI of the area of concern to confirm results of bone scan. Preferred method for confirmation is MRI. |
| **No** | No new lesions present at follow-up. |
| **Unable to Evaluate (UE)** | Subject not assessed or incompletely assessed for new lesions. |

| Evaluation of Overall Time Point Response | | | |
|---|---|---|---|
| **Target Lesion TPR** | **Non-target lesion TPR** | **New lesion TPR** | **Overall TPR** |
| CR | CR or NA | No | CR* |
| CR | Non-CR/non-PD | No | PR* |
| CR | UE | No | PR* |
| PR | Non-PD or NA or UE | No | PR* |
| SD | Non-PD or NA or UE | No | SD |
| UE | Any except PD | No | UE |
| PD | Any | No or Yes | PD |
| Any | PD | No or Yes | PD |
| Any | Any | Yes | PD** |
| NA | CR | No | CR* |
| NA | Non-CR/Non-PD | No | Non-CR/non-PD |
| NA | UE | No | UE |

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease, TPR, time point response; UE, unable to evaluate; NA, not applicable (no such lesions at screening); Any, CR, PR, SD, PD, NA, or UE.

The overall response at a given time point does not depend upon the overall response assigned at any prior or subsequent time point (ie, confirmation requirement are not considered when assigning time point responses).

* Subjects with an overall response of CR or PR must have a repeat tumor assessment performed no less than 4 weeks after the criteria for response are first met. However, the presence or absence of confirmation is not considered when assigning a time point response.

** 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.

**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, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. However, the presence or absence of confirmation is not considered when assigning a time point response. Longer intervals as determined by the study protocol may also be appropriate.

**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 H: Immune-Related Response Criteria (irRECIST)

Immune-related Response Criteria (irRECIST) are adapted from Wolchock et al 2009 and Nishino et al 2013.

Key aspects of irRECIST for immune-related response assessment:

- New lesions:
  - New lesions after baseline do not necessarily define radiographic progression
  - New measurable lesions are added into the total tumor burden and followed at subsequent tumor assessments
  - Unmeasurable new lesions preclude complete response status
- Non-target lesions:
  - Non-target lesion progression does not define radiographic progression
  - Disappearance of all non-target lesions is required for complete response status
- Radiographic progression:
  - Is determined only on the basis of measurable disease
  - Is defined by a ≥ 20% increase of sum of lesion diameter (SLD; including measurable new lesions)
  - Radiographic progression that is not confirmed ≥ 4 weeks from the first date documented is not radiographic progression by immune-response criteria
  - Best response may occur after any number of radiographic progression assessments

**Evaluation of Overall Immune-related Time Point Response by irRECIST Criteria**

| Target Lesion TPR | Non-Target Lesion TPR | New Measurable Lesion | New Non-Measurable Lesion | % Change in irSLD Tumor Burden (Including Measurable New Lesions) | Overall Immune-Related TPR |
|---|---|---|---|---|---|
| CR | CR | No | No | -100% | irCR |
| PR | Any | Any | Any | ≤ -30% | irPR |
| SD | Any | Any | Any | > -30% to < +20% | irSD |
| PD | Any | Any | Any | ≥ +20% | irPD |

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease, ir, immune-related; SLD, sum of lesion diameter; TPR, time-point response.

Time point responses and best overall response per irRECIST, incorporating confirmation requirements, will be derived during statistical analysis from the tumor evaluations performed by the investigator.

## Appendix I: Infusion-Related Reaction and Cytokine-Release Syndrome Guidelines

| Event | Management |
|---|---|
| Grade 1 [a]<br>Fever [b] with or without constitutional symptoms | • Immediately interrupt infusion.<br>• Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset.<br>• If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate.<br>• If symptoms recur, discontinue infusion of this dose.<br>• Administer symptomatic treatment [c], including maintenance of IV fluids for hydration.<br>• In case of rapid decline or prolonged CRS (> 2 days) or in subjects with significant symptoms and/or comorbidities, consider managing as per Grade 2.<br>• 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]<br>Fever [b] with hypotension not requiring vasopressors<br>**and/or**<br>Hypoxia requiring low-flow oxygen [d] by nasal cannula or blow-by | • Immediately interrupt infusion.<br>• Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset.<br>• If symptoms recur, discontinue infusion of this dose.<br>• Administer symptomatic treatment. [c]<br>• For hypotension, administer IV fluid bolus as needed.<br>• 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.<br>• 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.<br>• Consider IV corticosteroids (eg, methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours).<br>• Consider anti-cytokine therapy. [e]<br>• Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, ie, hospitalize subject (monitoring in the ICU is recommended), permanently discontinue atezolizumab, and contact the Sponsor.<br>• 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.<br>• If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact the Sponsor. |

| Event | Management |
|---|---|
| Grade 3[a]<br>Fever[b] with hypotension requiring a vasopressor (with or without vasopressin) **and/or**<br>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]<br>• Administer symptomatic treatment.[c]<br>• For hypotension, administer IV fluid bolus and vasopressor as needed.<br>• 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.<br>• 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.<br>• Administer IV corticosteroids (eg, methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours).<br>• Consider anti-cytokine therapy.[e]<br>• Hospitalize subject until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, ie, admit subject to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for subjects who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator and in consultation with the Sponsor. |
| Grade 4[a]<br>Fever[b] with hypotension requiring multiple vasopressors (excluding vasopressin) **and/or**<br>Hypoxia requiring oxygen by positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation) | • Permanently discontinue atezolizumab and contact the Sponsor.[f]<br>• Administer symptomatic treatment.[c]<br>• Admit subject 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.<br>• 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.<br>• Administer IV corticosteroids (eg, methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours).<br>• Consider anti-cytokine therapy[e]. For subjects who are refractory to anticytokine therapy, experimental treatments[g] may be considered at the discretion of the investigator and in consultation with the Sponsor.<br>• Hospitalize subject until complete resolution of symptoms. |

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

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

[a] Grading system for management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE (version as specified in the protocol) 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 subjects who develop CRS and then receive antipyretic, anti-cytokine, or corticosteroid therapy, fever is no longer required when subsequently determining event severity (grade). In this case, the grade is driven by the presence of hypotension and/or hypoxia.

[c] Symptomatic treatment may include oral or IV antihistamines, 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 anti-cytokine therapy has been used for treatment of CRS with immune checkpoint inhibitors (Rotz et al 2017; Adashek and Feldman 2019), but data are limited, and the role of such treatment in the setting of antibody-associated CRS has not been established.

[f] Resumption of atezolizumab may be considered in subjects who are deriving benefit and have fully recovered from the event. Subjects can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Sponsor. 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 consulting the Sponsor and considering the benefit-risk ratio.

[g] Refer to Riegler et al (2019) for information on experimental treatments for CRS.

## Appendix J: Potential Drug Interactions with Cabozantinib

The Investigator should evaluate concomitant medications prior to initiation for potential drug interactions with cabozantinib through the CYP3A4 pathway. The table below shows examples of potential strong inhibitors and inducers of CYP3A4.

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

This table is not all-inclusive. Please refer to the FDA website for the most updated lists of substrates, inducers, and inhibitors of selected CYP450 isozyme pathways:

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

## Appendix K: Methods of Contraception

In Inclusion Criterion 9 (Study Synopsis and Protocol Section 4.2):

Sexually active fertile subjects and their partners must agree to use highly effective methods of contraception that alone or in combination result in a failure rate of less than 1% per year when used consistently and correctly during the course of the study and for 5 months after the last dose of study treatment. Such methods include:

- Placement of an intrauterine device (IUD)
- Placement of an intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence (the reliability of sexual abstinence needs to be evaluated in relation to the preferred and usual lifestyle of the subject)
- Combined (estrogen- and progestogen-containing) hormonal contraception*:
    - Oral
    - Intravaginal
    - Dermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation*:
    - Oral
    - Injectable
    - Implantable

* The effect of cabozantinib on the pharmacokinetics of contraceptive steroids has not been investigated. Because oral contraceptives might possibly not be considered as “effective methods of contraception,” they should be used together with another method.

Furthermore, male subjects must refrain from donating sperm in order to avoid transmission of study treatment in semen for the duration of study treatment and through 5 months after their last dose of study treatment.

## Appendix L: Child-Pugh Scoring System for Subjects with Chronic Liver Disease

Modified Child-Pugh classification of severity of liver disease (Pugh et al 1973, Lucey 1997) for subjects with chronic liver disease is according to the degree of ascites, total bilirubin and albumin, prothrombin time, and degree of encephalopathy. Each measure is scored 1-3, with 3 indicating greatest severity:

| | | **Points assigned** | |
|---|---|---|---|
| **Parameter** | **1** | **2** | **3** |
| Ascites | none | mild/moderate (diuretic-responsive) | tense (diuretic-refractory) |
| Total bilirubin, mg/dL | < 2 | 2–3 | > 3 |
| Albumin, g/dL | > 3.5 | 2.8–3.5 | < 2.8 |
| Prothrombin time | | | |
| Seconds over control | 1–3 | 4–6 | > 6 |
| *or* | | | |
| INR | < 1.7 | 1.7–2.3 | > 2.3 |
| Encephalopathy | none | Grade 1–2 (or precipitant-induced) | Grade 3–4 (chronic) |

Child-Pugh score (A, B, or C) based on total score from the above point assignments:

| **Grade** | **Points** | **1-year survival** | **2-year survival** |
|---|---|---|---|
| A: well-compensated disease | 5–6 | 100% | 85% |
| B: significant functional compromise | 7–9 | 80% | 60% |
| C: decompensated disease | 10–15 | 45% | 35% |

## Appendix M: COVID-19 Instructions

XL184-021 Protocol Amendment 6.0 describes contingencies and accommodations to address 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 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.

Under the exceptional circumstances of the COVID-19 pandemic where enrolled subjects are not able 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. 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 if applicable.

- 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.

Subjects who develop COVID-19 while on study may be allowed to continue study treatment if the Investigator determines that the risk-benefit ratio for the subject favors continuing treatment, and the Sponsor approves the decision. 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 an SAE using their clinical judgment. The investigator should further consider if the diagnosis meets the criteria of being a significant medical event.

When recording data missing, impacted, or related to COVID-19 in the electronic CRFs, the conventions below are to be employed. Refer to updated CRF Completion Guidelines and site communication memos for additional instructions on how to document data missing or impacted by COVID-19.

| **Case Report Form** | **Instructions** |
|---|---|
| Adverse Event CRF | • Record COVID-19 diagnoses as "COVID-19"<br>• Record suspected cases as "suspected COVID-19"<br>• If death is the outcome of such an event, the CTCAE grade should be assigned as '5'<br>See the CRF instructions on 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<br>• 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:<br>o Indicate "Other" as the reason for treatment discontinuation and describe the reason in the Specify field, including the term "COVID-19"<br>For example – Other, Specify: "Subject unable to travel due to COVID-19 restrictions"<br>• If study treatment ended primarily due to an AE caused by COVID-19 or suspected COVID-19:<br>o Indicate "AE/SAE unrelated to progression of disease under study"<br>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:<br>o Indicate "Other" as the reason for discontinuation and describe the reason in the Specify field, including the term "COVID-19"<br>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:<br>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".<br>o 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)<br>For example – Other, Specify: "Subject unable to travel due to COVID-19 restrictions" |