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# XL184-315: STATISTICAL ANALYSIS PLAN

# A PHASE 3, RANDOMIZED, OPEN-LABEL, CONTROLLED STUDY OF CABOZANTINIB (XL184) IN COMBINATION WITH ATEZOLIZUMAB VS SECOND NOVEL HORMONAL THERAPY (NHT) IN SUBJECTS WITH METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

Version 3.0

Date: August 9, 2023

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| ADA | Anti-drug antibodies |
| ADT | Androgen deprivation therapy |
| AE | Adverse event |
| AESI | Adverse event of special interest |
| ALP | Alkaline phosphatase |
| ALT | Alanine aminotransferase |
| ANC | Absolute neutrophil count |
| AST | Aspartate aminotransferase |
| ATA | Adequate tumor assessment |
| ATC | Anatomical Therapeutic Chemical |
| BID | Twice daily |
| BIRC | Blinded independent review committee |
| BMI | Body mass index |
| CI | Confidence interval |
| Cm | Centimeter |
| CNS | Central nervous system |
| CRF | Case report form |
| CSR | Clinical study report |
| CT | Computerized tomography |
| CTC | Circulating tumor cell |
| CTCAE | Common terminology criteria for adverse events |
| CTMS | Clinical trial management system |
| DBP | Diastolic blood pressure |
| EBRT | External beam radiation therapy |
| ECG | Electrocardiogram |
| ECOG PS | Eastern Cooperative Oncology Group Performance Status |
| eGFR | Epidermal growth factor receptor |
| EORTC | European Organization for Research and Treatment of Cancer |
| EQ-5D-5L | EuroQol 5 Dimension 5 Level |
| ER | Emergency room visit |
| ETM | Events to monitor |
| FDA | Food and Drug Administration |
| FU-1(2) | Follow-up visit 1(2) |
| HCRU | Health care resource utilization |

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| | |
|---|---|
| HGB | Hemoglobin |
| HR | Hazard ratio |
| HRQOL | Health-Related Quality of Life |
| ICH | International Conference on Harmonization |
| ICU | Intensive care unit |
| IDMC | Independent Data Monitoring Committee |
| IF | Information fraction |
| INR | International normalized ratio |
| irAE | Immune-related adverse events |
| IRT | Interactive Response Technology |
| ITT | Intent-To-Treat |
| IV | Intravenous |
| JNC | Joint national committee |
| kg | Kilogram |
| LDH | Lactate dehydrogenase |
| LD-OF | Lan-DeMets O'Brien-Fleming |
| LLQ | Lower limit of quantitation |
| M0 | Non-metastatic |
| (m)CRPC | (Metastatic) castration-resistant prostate cancer |
| (m)CSPC | (Metastatic) castration-sensitive prostate cancer |
| MedDRA | Medical Dictionary for Regulatory Activities |
| | |
| mg | Milligram |
| mmHg | millimeters of mercury |
| MRI | Magnetic resonance imaging |
| NA | Not applicable |
| NCI | National Cancer Institute |
| NHT | Novel hormonal therapy |
| NPACT | Nonprotocol anticancer therapy |
| NRS | Numeric rating scale |
| OS | Overall survival |
| ORR | Objective response rate |
| PCWG3 | Prostate Cancer Working Group 3 |
| PD | Progressive disease |
| PFS | Progression-free survival |

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| | |
|---|---|
| PITT | PFS Intent-to-Treat |
| PK | Pharmacokinetic |
| po | Per os (by mouth) |
| PSA | Prostate-specific antigen |
| PT | Preferred term |
| Q3W | Every 3 weeks |
| qd | Once daily |
| qod | Every other day |
| QOL | Quality of Life |
| QTcF | Corrected QT interval by Fridericia |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| RSV | Routine safety visit |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SAS | Statistical analysis software |
| SBP | Systolic blood pressure |
| SD | Stable Disease |
| SE | Standard error |
| SOC | System organ class |
| SSE | Symptomatic skeletal events |
| TEAE | Treatment-emergent adverse event |
| TSH | Thyroid stimulating hormone |
| TTE | Time to event |
| ULN | Upper limit of normal |
| ULQ | Upper limit of quantitation |
| UPCR | Urine protein/creatinine ratio |
| VAS | Visual analogue scale |
| WBC | White blood cell |
| WHO-DD | World Health Organization drug dictionary |

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# 1. ADMINISTRATIVE STRUCTURE AND VERSION HISTORY

Exelixis, Inc. is sponsoring this study. Exelixis is responsible for the statistical design and planning of this study. Statistical programming and analyses are being conducted under contract by Allucent (previously known as CATO-SMS) Inc. in conjunction with Exelixis, Inc.

This version of the Statistical Analysis Plan (SAP) is based on Protocol Amendment 5.0 dated 24 January 2023.

**Table 1: Statistical Analysis Plan Version History**

| Date | Version | Primary Reason(s) for Amendment |
|---|---|---|
| 28 Nov 2022 | 1.0 (Based on Protocol Amendment 4.0) | Not Applicable |
| 25 May 2023 | 2.0 (Based on Protocol Amendment 5.0) | • Ukraine subjects (24) were excluded from efficacy and safety analyses to address impact of the Ukraine War on treatment effect estimands following principal stratum strategy.<br>• Analysis populations were modified to exclude Ukraine subjects: OS, ORR and other efficacy endpoints will be analyzed in modified ITT (mITT) Population, safety analyses will be conducted in modified safety analysis (mSafety) Population; separate summary tables and listings will be provided for Ukraine subjects.<br>• The PITT Population was expanded following the rule prespecified in protocol that the PITT "Population may be extended to the first 400 subjects randomized if a review of accumulating events suggests that the number of events required may not (or may take much longer than expected to) be reached (due to permanent censoring) among the first 324 subjects originally planned."<br>• The PITT Population was expanded to the 376 subjects among the first 400 randomized excluding all 24 Ukraine subjects. Primary PFS analysis will be conducted in PITT Population.<br>• Enrollment rate was updated to reflect the slower than expected enrollment.<br>• Planned study duration, time for enrollment, expected PFS and OS analysis time, and expected OS IA1 information fraction were updated due to slower than expected enrollment and expanded PITT Population.<br>• Clarification was added that to maintain study equipoise, the primary PFS analysis will not be |

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| Date | Version | Primary Reason(s) for Amendment |
|---|---|---|
| | | conducted before enrollment of approximately 580 subjects is completed.<br>• PFS and OS estimands were revised to clarify how the intercurrent event of Ukraine War was handled for each estimand. Additional alternative OS estimand was added.<br>• It was clarified that the primary PFS analysis will be conducted using all PFS events by BIRC in the non-Ukraine PITT Population (N=376) occurred before clinical cutoff date. Additional supportive analyses include: first 202 PFS events by BIRC in this population; all PFS events by BIRC in the first 300 randomized subjects (including Ukraine subjects); all PFS events by BIRC in the mITT Population.<br>• It was clarified that the anticancer therapy ADT is collected in prior and concomitant medications CRF page and will be summarized as part of prior and concomitant medications.<br>• It was clarified that dose modifications do not include infusion interruptions, which are not collected as AE outcome per CRF.<br>• The stratification factor collapsing algorithm was clarified for mITT Population.<br>• It was clarified that HRQOL analyses before the initiation of systemic nonprotocol anticancer therapy and prior to the end of study treatment will be included in the analysis.<br>• Details about biomarker analysis were added.<br>• Baseline renal failure summary was removed as such information will be presented as deviations from protocol I/E criteria.<br>• The following analyses were removed as such data were not collected in CRF:<br>o Subjects with a Related Grade 5 TEAE at any time after first dose date and ≤ 30 (100) days of last dose of any study treatment component and not causally related to disease under study.<br>• SAEs will be summarized in the extended safety observation period as well as the standard safety observation period.<br>• Subgroup analyses (Section 8.7) for general AE and SAE were added. |

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| Date | Version | Primary Reason(s) for Amendment |
|---|---|---|
| 09 Aug 2023 | 3.0 (Based on Protocol Amendment 5.0) | The SAP was amended based on Type C meeting feedback received from FDA on Jul 20th "Simply excluding patients impacted from the Ukraine war is not a typical strategy. In general, efficacy analyses should be based on randomized patients (i.e., PFS analysis based on 400 patients randomized, OS analysis based on 507 patients randomized)", and FDA suggested sensitivity analyses including censoring when the war started, using treatment policy strategy, and excluding Ukraine subjects.<br>• Primary analyses changed from excluding to including Ukraine subjects for efficacy and safety analyses<br>• Original primary analyses planned in Version V2.0 to exclude Ukraine subjects for PFS, OS and ORR are changed to sensitivity analyses for PFS, OS and ORR<br>• Added sensitivity analyses of PFS, OS and ORR by censoring at the start of war (24 February 2022) for Ukraine subjects on PFS-EP-1<br>• Removed definition of mITT and mSafety, as analyses will be done without excluding Ukraine subjects<br>• Section 5.3 Demographic and Baseline Characteristics:<br>o Sex category removed "Not reported" as not collected in CRF<br>o Sites of qualifying measurable disease were classified in 4 subcategories<br>• In Section 7.5.3, clarified the analysis per PCWG3 is similar to that for PFS-EP-1<br>• Lab parameters summarized for baseline and abnormalities clarified<br>• Other editorial changes for clarification purpose, which does not impact analysis, including ORR will be primarily analyzed on subjects with measurable disease in ITT followed for at least 6 months, censoring rule of missing 2 or more consecutive tumor assessments immediately prior to PD or deaths, at least one timepoint tumor response of SD must be documented ≥ 42 days after randomization for BOR categorized as SD. |

ADT = androgen deprivation therapy; BIRC = Blinded Independent Review Committee; BOR = best overall response; HRQoL = Health-Related Quality of Life; OS = Overall survival; ORR=overall response rate; PCWG3 = Prostate Cancer Working Group 3; PFS = progression-free survival; PITT = PFS Intent-to-Treat.

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# 2. STUDY DESCRIPTION

## 2.1. Study Design

This is a Phase 3, multicenter, randomized, parallel-group, open-label, controlled study of the combination of cabozantinib (40 mg po qd) with atezolizumab (1200 mg IV q3W) versus second novel hormonal therapy (NHT [abiraterone or enzalutamide]) in subjects with metastatic castration-resistant prostate cancer (mCRPC [adenocarcinoma]) who previously received one, and only one, NHT (eg, abiraterone, apalutamide, darolutamide, or enzalutamide) to treat metastatic castration-sensitive prostate cancer (mCSPC [including locally advanced M0 CSPC]), M0 CRPC, and/or mCRPC. Progression-free survival (PFS) and overall survival (OS) are the multiple primary endpoints. The primary analysis of PFS per Response Evaluation Criteria in Solid Tumors (RECIST 1.1) will be based upon radiographic assessments by Blinded Independent Review Committee (BIRC). Approximately 580 eligible subjects with mCRPC with measurable visceral metastasis or measurable extrapelvic lymphadenopathy, and whose disease is deemed to be worsening based on prostate-specific antigen (PSA) or radiographic soft tissue progression, in the opinion of the Investigator, will be randomized at approximately 280 sites in this study.

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

### 2.1.1. Pre-Treatment Period:

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

### 2.1.2. Treatment Period:

Subjects who meet all study eligibility criteria will be randomly assigned in a 1:1 fashion to receive cabozantinib plus atezolizumab (N=290) or second NHT (N=290), respectively. Based on treatment assignment, subjects will begin treatment on one of the following regimens:

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

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Randomization will be stratified by the following factors:

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

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

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

Crossover among treatment arms will not be allowed.

### 2.1.3. Post-Treatment Period:

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

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

### 2.1.4. Study Completion:

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

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### 2.1.5. Maintenance Phase/Treatment After Study Completion

The purpose of the Maintenance Phase is to continue to provide long-term access to study drug(s) to subjects who are deriving clinical benefit even after the study objectives have been completed (study completion, see Section 2.1.4). When sufficient data have been collected to adequately evaluate all study endpoints, the Sponsor may initiate a Maintenance Phase. Upon initiation of the Maintenance Phase, the Sponsor considers the safety and efficacy profile of the experimental treatment regimen within this study to have been sufficiently established, and data analyses required for regulatory purposes to have been completed. The Sponsor is to notify the sites if or when the study will enter the Maintenance Phase or if an alternative post-study completion option will be implemented. In the Maintenance Phase, subjects on study treatment will continue to receive the study treatment(s) to which they were randomized until they meet a protocol-defined criterion for treatment discontinuation.

Only data collected prior to initiation of the Maintenance Phase will be reported in the clinical study report (CSR), as the clinical database will be closed upon initiation of this phase. Important safety data (see protocol for details) collected during this phase will be captured in the safety database.

### 2.1.6. End of Trial

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

## 2.2. Study Treatment

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

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

## 2.3. Study Objectives and Endpoints

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

### 2.3.1. Primary Efficacy Endpoints

The 2 primary efficacy endpoints are:

- Duration of progression-free survival (PFS) per RECIST 1.1 per BIRC

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- Duration of overall survival (OS)

### 2.3.2. Secondary Efficacy Endpoints

- Objective response rate (ORR) per RECIST 1.1 per BIRC

### 2.3.3. Additional Endpoints

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

## 2.4. Power and Sample Size Justification

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

The Ukraine War started on 24 February 2022, when 24 subjects had already been enrolled from Ukraine but most subjects had not yet progressed or died. The war has had a multifaceted impact on the integrity of the data involving subjects from Ukraine, including a substantial proportion of the 24 Ukrainian-enrolled subjects being unable to access study drugs, undergo protocol-required

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safety and imaging assessments, and have their data entered into EDC, for a protracted period. Additionally, source data verification has been significantly impacted due to the war; data collected both before and after war initiation are compromised. In Protocol Amendment 3.0 dated 02 June 2022, the original Progression-free Survival Intent-to-Treat (PITT) Population was expanded from the first 300 to 324 randomized subjects to mitigate potential loss of Ukraine subjects data. However, the study is designed to evaluate treatment effects (estimands) in the absence of such disruptions caused by the war (EMA, 2022). Therefore, sensitivity analyses for PFS, OS and ORR by applying a hypothetical estimand approach and principle stratum estimand approaches, separately, will be performed for Ukraine subjects for the intercurrent event of the Ukraine War.

A blinded review of accumulating events suggested that the number of events required would take much longer than expected to be reached due to slower than expected enrollment. Following the rule prespecified in Protocol Amendment 3.0 dated 02 June 2022 that the PITT "Population may be extended to the first 400 subjects randomized if a review of accumulating events suggests that the number of events required may not (or may take much longer than expected to) be reached (due to permanent censoring) among the first 324 subjects originally planned", the PITT Population is expanded to the first 400 randomized subjects. The minimum number of events targeted to perform this event-driven analysis will not change; thus, this increase would have no impact on study power, Type 1 error, criteria for statistical significance, or the minimum effect size that rejects the null hypothesis. But the PITT sample size and analysis time are adjusted accordingly.

For PFS, a total of 202 events among the first 400 randomized subjects, in the combination and second NHT control arms provide the study with 90% power for a 2-sided log-rank test with a 0.002 level of significance to detect a hypothesized true hazard ratio (HR) of 0.54. Assuming an exponential distribution of PFS, this corresponds to an 85% increase in median PFS from 4 months to 7.4 months. In the current design, the minimum observed effect that would result in statistical significance for PFS is a HR of 0.65, a 55% improvement in median PFS from 4 to 6.2 months.

For OS, a total of 340 deaths among all 580 subjects randomized in the combination and second NHT arms is required to provide 90% power to detect an HR of 0.70 using the log-rank test and a 2-sided significance level of 0.048. Assuming an exponential distribution for OS, this corresponds to a 43% increase in median survival from 14 months to 20 months. Under this design, the minimum observed effect that would result in statistical significance for the primary analysis of OS is a HR of 0.80, a 25% improvement in median from 14 to 17.5 months.

Two interim analyses of OS are planned. The first interim analysis of OS will be conducted at the time of the primary analysis of PFS. This is expected to occur at approximately the 45% information fraction for OS, an update from the originally expected 32% due to the later-than-expected primary PFS analysis time. The second interim analysis of OS is planned at approximately the 76% information fraction. Inflation of Type 1 error associated with these interim analyses will be controlled using Lan-DeMets O'Brien-Fleming (LD-OF) alpha-spending functions based upon a total alpha allocation for OS that depends upon whether the PFS result is significant.

With an average accrual rate of approximately 24 subjects per month (3 subjects per month for 5 months, 26 subjects per month from 6 to 15 months, and 37 subjects per month from Month 16

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onward) and using a 1:1 treatment allocation ratio among the experimental and control arms, a total of approximately 580 subjects (290 subjects in each arm) is required to observe the required number of events within the planned study duration (approximately 24 months accrual; approximately 21 months to observe the required PFS events and approximately 37 months to observe the required deaths for OS). These estimates are based upon the statistical assumptions, adjusted to accommodate the time required for all study sites to be activated and for subject recruitment to reach full potential. The true intervals required to meet these milestones may be longer or shorter due to divergence from assumptions, or due to the impact of the global COVID-19 pandemic on subject enrollment and other aspects of study conduct. The estimates for the timing of event-driven analyses do not include the additional months required for event ascertainment, data quality review, data analysis and interpretation. The study sample size may be increased up to an additional 25% if a review of the accumulating data suggests that the COVID-19 pandemic has caused the rate of study dropout or noncompliance to increase to a degree that the ability to adequately evaluate study endpoints may be undermined.

The actual enrollment was slower than expected (average approximately 17 subjects per month, 6 subjects per month for 5 months, 20 subjects per month from Month 6 and onward). The enrollment time and analysis time are updated to reflect the slower enrollment speed, the expansion of the PITT Population.

An overview of the endpoints and operating characteristics is shown in Table 2.

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**Table 2: Summary of Endpoint Operating Characteristics**

| Accrual per month | 6/month until 5 months, 20/month from 6 months onward | |
|---|---|---|
| Randomization allocation | 1:1 | |
| **Endpoint:** | **PFS: Primary Endpoint** | **OS: Primary Endpoint** |
| Power | 90% | 90% |
| Alpha allocated (2-sided) | 0.002 | 0.048 |
| Number of interim analyses (approximate information fraction) | 0 (NA) | 2 (45%, 76%) |
| Assumed median control vs experimental (months) | 4 vs 7.4 | 14 vs 20 |
| Assumed HR | 0.54 | 0.70 |
| Number of events | 202 | 340 |
| N for analysis | 400 (PITT Population) | 580 (ITT Population) |
| Time to enroll (months) | 23 | 32 |
| Time to trigger event (months) | 27 | 44 |
| Maximum HR to reject Ho (experimental median in months) | 0.65 (6.2) | 0.80 (17.5) |

Ho = null hypothesis; HR = hazard ratio; ITT = modified Intent-to-Treat; NA= not applicable; OS = overall survival; PFS = progression-free survival; PITT = PFS Intent-to-Treat.
* Accrual: 6/month until 5 months, 20/month from 6 months onward.

## 2.5. Randomization and Blinding

This is a multicenter, randomized, open-label, controlled Phase 3 study. The study treatment assignment will be known to the subjects, investigators, study centers, Sponsor, and any Contract Research Organization affiliated with the study other than the BIRC. Study staff supporting the BIRC will ensure that the blind is maintained for the BIRC. Reviewing aggregated efficacy data is not allowed except for prespecified formal analyses.

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

Eligible subjects will be randomly assigned in a 1:1 ratio to the 2 study treatment arms (see Section 2.2).

Stratified randomization will be conducted using permuted blocks over 12 strata. The 12 strata are based on all combinations of the 3 stratification factors, which will be established at screening.

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If at least one stratum has fewer than 20 subjects in the PITT Population, a strata-collapsing algorithm will be implemented. The order of collapsing is to first combine the mCSPC and M0 CRPC levels of prior NHT indication, followed by collapsing all levels of prior NHT indication, prior docetaxel, and liver metastasis, respectively. The same strata-collapsing algorithm will be applied if at least one stratum has fewer than 20 subjects in the ITT Population. The final set of stratification factors used for the multiple primary endpoints will be applied to all other endpoints where stratified analyses are planned. The stratification factors will be obtained from the IRT at the time of randomization.

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

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

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# 3. ANALYSIS POPULATIONS

The planned primary analysis populations for the statistical analyses are briefly summarized in Table 3. Further information on these populations is provided in the sections below. Sensitivity analysis populations are described within each endpoints.

**Table 3: Analysis Populations**

| Analysis | Population | Subjects |
|---|---|---|
| Primary PFS | PITT | PFS-ITT Population: first 400 subjects randomized. |
| Primary OS | ITT | ITT Population: All randomized subjects. |
| Secondary efficacy ORR | ITT | Subjects who have measurable disease at baseline and are followed for at least 6 months in the ITT Population. |
| Additional efficacy analyses | ITT | ITT Population: All randomized subjects. |
| Safety analyses | Safety | Safety Population: All subjects who received any study treatments. |
| PK analyses | PK | PK Population: All subjects who received any dose of atezolizumab or cabozantinib and who have available PK data. |

ITT = Intent-to-Treat; OS = overall survival; PFS = progression-free survival; PITT = PFS Intent-to-Treat; PK = pharmacokinetic; ORR = objective response rate.

## 3.1. Intent-to-Treat Population

The ITT Population will consist of all subjects who are randomized regardless of whether any study treatment or the correct study treatment is received.

## 3.2. Progression-Free Survival Intent-to-Treat Population (PITT)

The first 400 randomized subjects (based upon Greenwich Mean Time randomization date/time values) to the experimental arm or control arm will be considered as the PITT Population.

## 3.3. Safety Population

The Safety Population will consist of all subjects who receive any amount of study treatment. Analyses based on the Safety Population will be performed according to the actual treatment received for the length of the study. Subjects who receive at least one dose of experimental arm treatment will be included in the experimental arm.

## 3.4. P-Safety Population

The P-Safety Population will include subjects in the PITT Population who are in the Safety Population. Select summaries will be presented based on actual treatment received.

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# 4. GENERAL CONVENTIONS

The statistical principles applied in the design and planned analyses of this study are consistent with International Conference on Harmonization (ICH) E9 and draft E9 R1 guidelines (ICH 1998 and 2019) and FDA's Guidance for Industry on Multiple Endpoints in Clinical Trials (2017) and for handling Clinical Trial Endpoints for Approval of Cancer Drugs and Biologics (2018).

Continuous data will be summarized using descriptive statistics (number of observations, mean, standard deviation, median, 25$^{th}$ and 75$^{th}$ percentiles, minimum, and maximum). Frequencies and percentages will be used for summarizing categorical (discrete) data. Missing values of categorical data will be presented under "Missing" category.

Confidence intervals (CIs), when presented, will generally be constructed at the 95% level. For binomial variables, the Clopper-Pearson method (Clopper and Pearson 1934) will be employed unless otherwise specified.

A month is operationally defined to be 30.4375 days.

Efficacy summaries will be presented by treatment arm randomized to and safety summaries by treatment received unless otherwise specified.

## 4.1. Analyses and Reports

Up to 4 study analyses are planned over the course of the study:

1. Primary PFS and 1$^{st}$ interim OS analysis. (To maintain study equipoise, this analysis will not be conducted before enrollment of approximately 580 subjects is completed.)
2. Second interim OS if 1$^{st}$ interim OS is not successful.
3. Final OS, if 1$^{st}$ and 2$^{nd}$ interim OS are not successful.
4. Final safety update, upon initiation of the Maintenance Phase.

Details on the control of Type 1 error and interim analyses of OS are provided in Sections 7.2 and 7.3.

## 4.2. Definition of Baseline

In general, for efficacy endpoints, the last-observed measurement prior to randomization will be considered the baseline measurement. An exception to this rule is efficacy biomarkers such as pharmacogenetic blood samples, biomarker samples, bone marker samples, and blood samples for potential circulating tumor cell (CTC) analyses. These samples, per schedule of assessments, are to be collected on RSV1 (which could be up to 3 days after randomization) but prior to the administration of the first dose; hence, baseline for these measurements will be defined with respect to the first dose date. For subjects who did not receive any study treatment, last-observed biomarker sample available prior to randomization will be considered as the baseline observation.

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For safety endpoints, the last-observed measurement on or before the first dose of study treatment will be considered the baseline measurement unless otherwise specified and will be established for each period defined in Section 4.6.

For endpoints related to healthcare utilization, pain assessments, HRQOL (EQ-5D-5L and QLQ-C30), the last observation on or before the first dose of study treatment will be considered the baseline measurement unless otherwise specified. These endpoints, per schedule of assessments, are to be collected on RSV1 (which could be up to 3 days after randomization) but prior to the administration of the first dose; hence baseline for these measurements will be defined with respect to the first dose date. For subjects who did not receive any study treatment, last-observed measurement available up to 3 days after randomization will be considered as the baseline observation.

For assessments on the day of first dose of study treatment where time is not captured, if such procedures are required by the protocol to be conducted before the first dose or a nominal pre-dose indicator is available, this will serve as sufficient evidence that the assessment occurred prior to first dose.

The earliest instance of administration of any study treatment will be considered as the time point of first dose. Similarly, the latest instance of administration of any study treatment will be considered as the time point of last dose of study treatment.

## 4.3. Definition of Study Day

For efficacy data summaries, study day is defined with respect to the randomization date. For visits (or events) that occur on or after randomization, study day is defined as (date of visit [event] – date of randomization + 1). For visits (or events) that occur prior to randomization, study day is defined as (date of visit [event] – date of randomization). There is no study Day 0.

For safety data summaries, study day is defined with respect to the date of first dose of study treatment received. For visits (or events) that occur on or after first dose, study day is defined as (date of visit [event] – date of first dose of study treatment + 1). For visits (or events) that occur prior to first dose, study day is defined as (date of visit [event] – date of first dose of study treatment). There is no study Day 0.

For listings (such as for adverse events [AEs]) that include the derivations of "days since last dose," this is defined for each agent as (event date – date of last dose for the agent +1). Two such fields will be presented for subjects receiving the combination of agents. Events that occur on the same day as the last dose of a particular study treatment will therefore be described as occurring day one from the last dose of that study treatment.

## 4.4. Visit Window Calculation

Analyses will be according to actual visit dates and times. The planned analyses do not require the calculation of visit windows. However, for analyses that require a particular visit as planned, measurements included in that visit must have occurred during the acceptable window defined for the visit in the protocol, unless otherwise specified in this plan.

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## 4.5. Missing and Partial Data

In general, other than for partial dates, missing data will not be imputed and will be treated as missing. The algorithms for imputation of partial dates vary depending upon the parameter. Data imputation rules are presented in Appendix A.

## 4.6. Safety Observation Periods

Generally, only the safety data (including AEs that start or worsen, laboratory results, vital signs, ECGs, ECOG PS, concomitant medications, etc.) reported during a safety observation period (defined below) will be analyzed and summarized, unless otherwise specified in this plan.

### 4.6.1. Standard Safety Observation Period

The standard safety observation period is the interval from the first dose date of study treatment to the earliest of:

- Date of last dose of any component of study treatment + 30 days, or
- Date of death, or
- Date subject lost-to-follow up or withdrew consent, or
- Data cutoff date for analysis under consideration.

The standard safety observation period will be used for the analysis of general AEs, ETMs, and laboratory assessments, unless specified otherwise.

### 4.6.2. Extended Safety Observation Period

To evaluate the incidence of immune-related adverse events (irAEs), the extended safety observation period is defined as the interval from the first dose date of study treatment to the earliest of the following:

- Date of last dose last component of study treatment + 100 days, or
- Date of death, or
- Date subject lost-to-follow up or withdrew consent, or
- Data cutoff date for analysis under consideration.

In addition, Grade 5 AEs, and SAEs will be summarized using the extended safety observation period. Grade 5 AEs and SAEs will also be summarized on standard safety observation period.

## 4.7. Definition of Prior, Concomitant, and Subsequent Therapy

For inclusion in summary tables, incomplete start and stop dates for therapies (medications, radiation therapies, or surgery) will be imputed as detailed in Appendix A. Therapies may be summarized as prior, concomitant, and/or subsequent.

Based on imputed start and stop dates:

- Prior therapies (medications, radiation therapies, or surgery) are defined as medications with a start date occurring before the date of first dose of study treatment.

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- Concomitant therapies (medications, radiation therapies, or surgery) are defined as those that stop or continue after the date of the first dose through the end of the safety observation period.
- Concomitant and subsequent nonprotocol anticancer therapies (medications, radiation therapies, or surgery given in context of NPACT) are defined as those that start after the date of randomization.

## 4.8. Software

All analyses will be conducted using SAS Version 9.4 or higher.

## 4.9. Changes to Planned Analyses

Substantive changes to the analyses described in the protocol or in approved versions of this plan will be fully documented in a revised version of this plan approved by the Sponsor prior to conducting analyses.

Clarifications, minor corrections, and operational considerations necessary to accurately conduct the analyses that do not materially change the nature of the analysis will be documented in an addendum to this plan that will also be approved by the Sponsor prior to primary PFS analyses.

### 4.9.1. Expansion of PITT Population

The PITT Population was expanded to the first 400 randomized subjects. Detailed explanation could be found in Section 2.4 “Power and Sample Size Justification”.

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# 5. STUDY POPULATION SUMMARIES

## 5.1. Enrollment

Subjects are considered to be enrolled when randomized. Enrollment will be summarized by region, country, site, and protocol version for the PITT and ITT Populations.

## 5.2. Disposition

Subject disposition will be summarized categorically and will include the number and percentage of subjects in the PITT, ITT, Safety, and P-Safety Populations. A separate summary of all the 24 Ukraine subjects will be provided.

The following summaries will be presented:

- Number and percentage of subjects in the PITT, ITT, Safety, and P-Safety Populations
- Subjects treated with cabozantinib plus atezolizumab
- Subjects treated with abiraterone plus prednisone, or enzalutamide
- Subjects still on any treatment component(s) at the time of data cutoff
- Subjects who discontinued any study treatment component
- Subjects who discontinued all study treatment components
- Primary reason for discontinuation from:
  - Cabozantinib
  - Atezolizumab
  - Abiraterone
  - Enzalutamide
- Primary reason for discontinuation from radiographic follow up
- Primary reason for discontinuation from survival follow up

Number of subjects who screen failed and the reason for screen failure will also be presented.

## 5.3. Demographic and Baseline Characteristics

Summaries of demographics, stratification factors, and baseline characteristics will be presented for subjects in the PITT, ITT, Safety, and P-Safety Populations. A separate summary of all the 24 Ukraine subjects will be provided.

[A] The demographic characteristics include:

- Age (continuous)
- Age category 1:
  - $< 65$ years
  - $\geq 65$ years

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- Age category 2:
  - < 75 years
  - ≥ 75 years
- Age category 3:
  - < 65 years
  - 65 to < 75 years
  - 75 to < 85 years
  - ≥ 85 years
- Sex:
  - Male

- Ethnicity:
  - Hispanic or Latino
  - Not Hispanic or Latino
  - Not Reported
- Race:
  - American Indian or Alaska Native
  - Asian
  - Black or African American
  - Native Hawaiian or Other Pacific Islander
  - White
  - Multiple
  - Not Reported
  - Other
- Geographic Region:
  - North America
  - Europe
  - Asia Pacific
  - Latin America

Note: for this study birth date is not collected but age in years is collected at informed consent.

[B] Categorical summaries of the following stratification factors will be presented as recorded in the IRT during randomization and per the CRF:

- Liver metastasis (yes/no)
- Prior docetaxel for locally advanced or metastatic CSPC (yes/no)
  - Response is “no” if subject previously had M0 CRPC

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- First NHT given for mCRPC vs M0 CRPC vs mCSPC. Note: For subjects who have received the same NHT for both mCRPC and either mCSPC (including locally advanced M0 CSPC) or M0 CRPC, subjects should be stratified by the disease state for which they received their first NHT even if they did not progress on it.

[C] Baseline characteristics include:

- Height in centimeter (cm) – descriptive statistics
- Weight in kilogram (kg) – descriptive statistics
- Body mass index (BMI) in $kg/m^2$, calculated as (weight in kg*10000)/(Height in $cm)^2$ – descriptive summary
- ECOG PS: 0, 1, Missing
- Tobacco use:
  - Current
  - Former
  - Never
- Alcohol use:
  - Current
  - Former
  - Never

[D] Baseline laboratories:

Selected baseline laboratory results will be summarized, including:

- Albumin (g/L): $< 35$, $\geq 35$
- Total bilirubin (µmol/L): $< 22.23$, $\geq 22.23$ to $< 29.07$, $\geq 29.07$
- Baseline PSA
- Lab tests included in the Table 17
- Creatinine Clearance, testosterone, and serum calcium

## 5.4. Medical History

General medical history data will be coded per Medical Dictionary for Regular Activities (MedDRA).

## 5.5. Cancer History and Current Disease Status

Cancer history and current disease characteristics data collected on the cancer history CRF will be summarized categorically or with descriptive statistics as appropriate for the PITT and ITT Populations. A separate summary of all the 24 Ukraine subjects will be provided.

The following summaries are planned:

- Diagnosis of prostate adenocarcinoma as the primary histology (Yes, No)
- Secondary histology:

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  - Neuroendocrine differentiated
  - Small cell
  - Other
- Disease stage at the time of initial diagnosis:
  - Localized
  - Metastatic
- Summary of primary Gleason score, secondary Gleason score, and total Gleason score
- Time in years from initial diagnosis of prostate cancer to randomization
- PSA progression at screening (Yes, No)
- Soft-tissue disease progression (Yes, No)
- Summaries for tumor assessment at screening per Investigator and BIRC are:
  - Sites of disease at baseline
    - Bone
    - Lymph nodes
    - Brain
    - Visceral
      - Adrenal
      - Kidney
      - Liver
      - Lung
      - Spleen
      - Pancreas
    - Other
  - Sites of qualifying measurable disease:
    - Measurable extrapelvic visceral disease only
    - Measurable extrapelvic adenopathy only
    - Both
    - None
  - Number of target lesions (0, 1, 2, 3, 4, 5)
  - Number of organs with non-target lesions (0, 1, 2, $\geq$ 3)
  - Number of tumor sites (1, 2, $\geq$ 3)

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- Descriptive summary for baseline sum of target lesion diameter (mm)

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# 6. TREATMENTS AND MEDICATIONS

## 6.1. Prior Systemic Non-Radiation Anticancer Therapy

The following will be summarized categorically or with descriptive statistics, as appropriate, for all subjects in the PITT and ITT Populations:

All prior systemic non-radiation anticancer agents will be summarized categorically by Anatomical Therapeutic Chemical (ATC) Class Text and World Health Organization Drug Dictionary (WHO-DD) substance preferred name by study treatment arm. All prior systemic non-radiation anticancer agents (first NHT) will be summarized as below:

- The time from the end of most recent systemic non-radiation anticancer (prior NHT) therapy to randomization will be summarized descriptively
- Descriptive statistics for duration of most recent prior systemic non-radiation anticancer therapy (prior NHT)
- Number of prior systemic non-radiation anticancer regimens per subject (1, 2, ≥ 3) and descriptive statistics
- Summary of prior NHT by setting of therapy mCSPC (including locally advanced M0 CSPC), M0 CRPC, and mCRPC:
    - Reason for discontinuation of prior NHT
    - PSA progression on prior NHT (Yes, No)
    - Time from biochemical (PSA) progression on first NHT to randomization
    - Radiographic progression on prior NHT (Yes, No)
    - Time from radiographic progression on first NHT to randomization will be summarized descriptively

## 6.2. Prior Radiation Therapy, Surgery, and Procedures

Data obtained from the history of radiation therapy and history of surgeries and procedures CRF will be summarized categorically or with descriptive statistics, as appropriate, for all subjects in the PITT and ITT Populations:

- Number of subjects who received prior radiation therapy
- Subject incidence of prior radiation therapy by indication (prostate cancer and other)
- Number of prior radiation therapies for prostate cancer per subject (1, 2, ≥ 3) and descriptive statistics
- Subject incidence of prior radiation therapy by type (external beam radiation therapy [EBRT], internal radiation therapy [brachytherapy], radioembolization, and other) for prostate cancer or other indications
- Subject incidence of prior radiation therapy by site (bone, soft tissue, unknown) for prostate cancer or other indications

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- Number and percent of subjects that received prior radiation by anatomic site(s)
- The time from the end of most recent prior radiation therapy for prostate cancer to randomization
- Number of subjects with prior surgeries/procedures (Yes, No)
- Number of prior surgeries for prostate cancer
- Subject incidence of prior surgery type (TURP, radical prostatectomy - retropubic with pelvic lymphadenectomy, radical prostatectomy - retropubic without pelvic lymphadenectomy, cryosurgery, bilateral orchiectomy, high-intensity focused ultrasound, ureteral stent, nephrostomy catheter placement, other)
- The time from the end of most recent surgery for prostate cancer to randomization will be summarized descriptively

## 6.3. Prior and Concomitant Medications (Excluding Anticancer Therapy)

Medications recorded on the CRFs will be coded using the WHO-DD. Prior and concomitant medications, other than prior and subsequent anticancer therapies, will be summarized by treatment group in the Safety Population by ATC and WHO-DD base substance preferred name. Concomitant and subsequent anticancer therapies are addressed in Sections 6.7 and 6.8, respectively.

Protocol requires ongoing androgen deprivation therapy (ADT) with a gonadotropin releasing hormone (GnRH) agonist/antagonist as a concomitant medication while on study treatment, if the subject has not undergone bilateral orchiectomy. Hence ADT by ATC and WHO-DD will be displayed as prior and concomitant medications under ATC code ‘Gonadotropin Releasing Hormone Analogues’.

### 6.3.1. Corticosteroid Use

A summary of prior and concomitant corticosteroid (systemic) use will be presented as below. The below summary for concomitant corticosteroid use will not include the prednisone that was taken with abiraterone as study treatment:

- Number of subjects with prior corticosteroid use
- Number of subjects with concomitant corticosteroid use
- Number of subjects with concomitant corticosteroid use for irAE(s)
- Number of subjects with concomitant high-dose corticosteroid use for irAE(s); high-dose is defined as ≥ 40 mg/day of prednisone or equivalent

## 6.4. Study Treatment Exposure

Study treatment exposure will be summarized descriptively and will include subjects in the Safety and P-Safety Populations. A separate summary of study treatment exposure for all 24 Ukraine subjects will be provided.

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Due to different treatment types (infusion vs oral tablet) and frequency of administration (q3w vs daily) between atezolizumab and cabozantinib, the exposure summaries for oral components and the infusion components will be presented separately. The study protocol allows subjects on the experimental arm to discontinue one component of the combination treatment but continue to receive the other component. The date of discontinuation along with reason for discontinuation will be recorded on separate CRFs for each component of the study treatment. Duration of any study treatment is defined as time from first dose to date of last dose or cutoff date.

The algorithms for calculating the various exposure parameters are described in Table 4 for overall dosing summaries.

**Table 4: Study Treatment Exposure Summary (Overall summary)**

| | **Cabozantinib** | **Atezolizumab** | **Abiraterone** | **Prednisone** | **Enzalutamide** |
|---|---|---|---|---|---|
| Number of infusions | NA | Sum of all infusions administered | NA | NA | NA |
| Average daily dose (mg/day) | Cumulative dose (mg) / (duration of exposure in days) | NA | Cumulative dose (mg) / (duration of exposure in days) | Cumulative dose (mg) / (duration of exposure in days) | Cumulative dose (mg) / (duration of exposure in days) |
| Percent dose intensity | 100*(average dose in mg/day) / (40 mg/day) | 100*(total mg received)/((last dose date - first dose date + 21)*(1200/21)) | 100*(average dose in mg/day) / (1000 mg/day) | 100*(average dose in mg/day) / (10 mg/day) | 100*(average dose in mg/day) / (160 mg/day) |
| Duration of exposure in months (including holds) | (Last non-zero dose date– first dose date +1) /30.4375 | (Last infusion date–first dose date +1)/30.4375 | (Last non-zero dose date - first dose date +1) /30.4375 | (Last non-zero dose date - first dose date +1) /30.4375 | (Last non-zero dose date - first dose date +1) /30.4375 |
| Duration of exposure in months (excluding dose holds) | (Last non-zero dose date– first dose date - total days with dose received of 0 mg during this interval + 1) /30.4375 | NA | (Last non-zero dose date – first dose date - total days with dose received of 0 mg during this interval + 1) /30.4375 | (Last non-zero dose date – first dose date - total days with dose received of 0 mg during this interval + 1) /30.4375 | (Last non-zero dose date – first dose date - total days with dose received of 0 mg during this interval + 1) /30.4375 |
| Overall duration of study treatment (including holds) | (Maximum (date of last non-zero dose of cabozantinib or atezolizumab) – date of first dose of study treatment + 1) / 30.4375 | | (Maximum (date of last non-zero dose of abiraterone /prednisone or enzalutamide) – date of first dose of study treatment + 1) / 30.4375 | | |

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For the experimental arm an overall summary will be provided separately as follows:

- Duration (in months) of exposure, calculated as [maximum (date of last non-zero dose of cabozantinib or atezolizumab) – date of first dose of cabozantinib/atezolizumab + 1) /30.4375].
- The number and percent of subjects who received at least one non-zero dose of cabozantinib > 4 weeks after final dose of atezolizumab (discontinuation of atezolizumab).
- The number and percent of subjects who received at least one dose of atezolizumab > 4 weeks after final non-zero dose of cabozantinib (discontinuation of cabozantinib).

## 6.5. Study Treatment Modifications

Treatment modifications (holds, delays, reductions, incomplete infusion) for study treatment will be summarized for the Safety Population. Only modifications due to AE(s) will be summarized by protocol-defined dose levels. Per protocol, cabozantinib, abiraterone and enzalutamide doses can be reduced, held, or discontinued; prednisone dose can only be held; while atezolizumab infusions can be incomplete, interrupted, delayed, or discontinued but the dose cannot be reduced. Therefore, for the experimental arm, dose reduction summaries apply only to the cabozantinib treatment component. For summarization, atezolizumab delays will be considered dose holds and will also be counted as dose modifications. Incomplete or interrupted atezolizumab infusions will also be summarized. Therefore, for the experimental arm (cabozantinib + atezolizumab), dose-hold and dose-modification summaries will be presented by individual treatment components as well as by combination.

The protocol allows dose reductions for cabozantinib, abiraterone, and enzalutamide as shown in Table 5.

**Table 5: Protocol-Defined Dose Levels for Cabozantinib, Abiraterone and Enzalutamide**

| Study Arm Treatment | Assigned Starting Dose | First Dose Level Reduction | Second Dose Level Reduction |
|---|---|---|---|
| Cabozantinib | 40 mg (qd) | 20 mg (qd) | 20 mg (qod) |
| Abiraterone | 1000 mg (qd) | 500 mg (qd) | NA |
| Enzalutamide | 160 mg (qd) | 120 mg (qd) | 80 mg (qd) |

NA = not applicable; qd = once daily; qod = every other day.

A. The following summaries will be presented:

i. For dose reductions due to AE(s) for cabozantinib, abiraterone, and enzalutamide

Categorical summaries for:

- Number of subjects with any dose reduction due to an AE
- Number of subjects who received each dose level category
- Lowest non-zero dose level category received (excluding dose holds)

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- The last dose level received (excluding dose holds)
- Time on each dose level received

Descriptive statistics for:

- Time from first dose date to the first incidence of first dose level reduction (days)
- Time from first dose date to the first incidence of second dose level reduction (days)

ii. Summaries for dose holds due to AE(s) for cabozantinib, abiraterone, prednisone, and enzalutamide:

- Frequency counts and percentages will be presented for these categories: < 7 days, ≥ 7 days and <14 days, ≥ 14 days and < 21 days, ≥ 21 days and < 28 days, ≥ 28 days and < 56 days, ≥ 56 days and < 84 days, and ≥ 84 days for any dose holds.
- Descriptive statistics for number of doses holds (0 mg dose level) due to an AE. Frequency counts and percentages will be presented for these categories: 1, 2, 3 and > 3.
- Descriptive statistics for total duration of all dose holds per subject due to an AE. Frequency counts and percentages will be presented for these categories: ≥ 7 days, ≥ 14 days, ≥ 21 days, ≥ 28 days, ≥ 56 days, and ≥ 84 days. Duration of each dose hold is calculated as (stop date of hold – start date of hold + 1).
- Descriptive statistics for duration of dose holds per subject due to an AE. Frequency counts and percentages will be presented for these categories: ≥ 7 days, ≥ 14 days, ≥ 21 days, ≥ 28 days, ≥ 56 days, and ≥ 84 days calculated as (stop date of hold – start date of hold + 1).
- Median time and range for time to first dose hold will be presented for these categories: ≥ 7 days, ≥ 14 days, ≥ 21 days, ≥ 28 days, ≥ 56 days, and ≥ 84 days. The time to dose hold is calculated as (start date of the hold – first dose date + 1).
- Median time and range for time to second dose hold will be presented for these categories: ≥ 7 days, ≥ 14 days, ≥ 21 days, ≥ 28 days, ≥ 56 days, and ≥ 84 days.

iii. Summaries for dose modifications (defined as a reduction or hold) due to AE:

- Frequency counts and percentages for subjects with any dose modifications
- Descriptive statistics for number of dose modifications. Frequency counts and percentages will be presented for these categories: 1, 2, 3 and > 3
- Descriptive statistics for time to the first dose modification
- Descriptive statistics for time to the second dose modification

B. The following summaries will be presented for atezolizumab:

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- Number of subjects with any incomplete infusion
- Number of subjects with any interrupted infusion
- Number of subjects with dose delay due to an AE. Frequency counts and percentages will be presented for these categories: 1, 2, 3 and > 3
- Frequency counts and percentages for total duration of any dose delay will be presented for these categories: ≥ 7 days, ≥ 14 days, ≥ 21 days ≥ 28 days, ≥ 56 days, and ≥ 84 days
- Frequency counts and percentages for duration any dose delay due to AE will be presented for these categories: ≥ 7 days, ≥ 14 days, ≥ 21 days, ≥ 28 days, ≥ 56 days, and ≥ 84 days
- Descriptive statistics for time to first dose delay due to AE
- Descriptive statistics for time to second dose delay due to AE

## 6.6. Study Treatment Noncompliance and Dosing Errors

Treatment noncompliance and dosing errors for reasons other than AE(s) will be summarized in the PITT, ITT, and Safety Populations, as well as for all the 24 Ukraine subjects. Frequency counts and percentages will be presented by treatment groups for:

- Subjects with dose hold/delay (0 mg) due to noncompliance, site/logistic error, or other reasons
- Subjects who received a dose > the maximum allowed dose level at any time due to noncompliance, site/logistic error, or other reasons
- Subjects who received a nonprotocol specified dose level (≤ the maximum allowed dose level) at any time due to noncompliance, site/logistic error, or other reasons

## 6.7. Concomitant and Subsequent Nonprotocol Anticancer Therapy (NPACT)

Concomitant and subsequent NPACT will be summarized by treatment group in the PITT and ITT Population as follows:

- NPACTs will be summarized by ATC text and WHO Drug base substance preferred name
- Time to first systemic NPACT from randomization will be summarized by descriptive statistics

## 6.8. Concomitant and Subsequent Surgeries/ Procedures/ Radiation/ Transfusions

Concomitant and subsequent surgery/procedures that impacted the target lesion(s) will be summarized by treatment group in the PITT and ITT Populations.

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Frequency counts and percentages will be presented for concomitant and subsequent radiation therapy indication, type, and site by treatment group in the PITT and ITT Populations.

Concomitant transfusions will be summarized by transfusion type and treatment group for subjects in the Safety Population.

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# 7. EFFICACY ANALYSES

Unless otherwise specified, PFS will be analyzed in the PITT Population, while OS, ORR and other efficacy endpoints will be analyzed in the ITT Population. Sensitivity analyses for PFS, OS and ORR will be conducted with assessments of Ukraine patients after the start of the Ukraine war on 24 February 2022 being censored/excluded using a hypothetical estimand approach, and separately with all 24 Ukraine subjects' data excluded using a principle stratum estimand approach. Additional sensitivity analyses for PFS and OS will also be conducted and are specified in the Section 7.1.1 and Section 7.1.2. Listings of tumor response, disease progression, and OS will be provided for all the 24 Ukraine subjects.

## 7.1. Primary Efficacy Endpoints

The two primary efficacy endpoints for this study are duration of PFS per RECIST1.1 per BIRC and duration of OS. Formal hypothesis tests are planned for these endpoints.

### 7.1.1. Duration of Progression-Free Survival

#### 7.1.1.1. Primary Estimand

The primary estimand for PFS is the difference in survival functions between treatment conditions in the duration of radiographic PFS in the targeted population:

- irrespective of the impact of the Ukraine war on Ukraine subjects
- irrespective of whether the assigned study treatment was given, reduced, delayed/interrupted, or discontinued
- irrespective of clinical deterioration
- irrespective of whether radiation was given to bone
- irrespective of surgical resection of non-target lesions
- had surgery to resect target tumor lesions not occurred
- had systemic nonprotocol anticancer treatment not been given
- had radiation to soft tissue not been given
- had not missed 2 or more consecutive adequate tumor assessments immediately prior to PD or death (ATAs; as defined in Section 7.1.1.4)

Estimands are derived as specified in Table 6.

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**Table 6: Estimand Definition and Rationale for Primary Estimand**

| Estimand attribute[a] | Primary definition | | Rationale (as needed) |
|---|---|---|---|
| Treatment | Experimental Arm: Cabozantinib (40 mg po qd) + atezolizumab (1200 mg IV q3w)<br>Control Arm: Abiraterone (1000 mg po qd) + prednisone (5 mg po bid), OR enzalutamide (160 mg po qd) | | — |
| Population | Subjects randomized into the study intended to include subjects with mCRPC who have previously received one, and only one, NHT | | The initial clause "Subjects randomized into the study intended to include…" is included to align the estimand with the application of the ITT principle expected by regulatory reviewers |
| Endpoint | Duration of radiographic PFS per RECIST 1.1 per BIRC | | — |
| Intercurrent events | **Event** | **Strategy** | **Rationale (as needed)** |
| | Start of Ukraine war on 24 February 2022 for Ukraine subjects | Treatment policy | This strategy applied to align the estimand with the application of the ITT principle expected by regulatory reviewers. |
| | Receipt of assigned study treatment, dose reduction and delay/interruption, and treatment discontinuation | Treatment policy | This strategy applied to align the estimand with the application of the ITT principle expected by regulatory reviewers. |
| | Clinical deterioration | Treatment policy | This strategy applied due to the nature of the primary endpoint, which is radiographic PFS. |
| | Receipt of local radiation to bone | Treatment policy | This strategy applied as local radiation to bone is typically palliative and does not directly confound radiographic evaluations of soft tissue. |
| | Surgical resection of non-target tumor lesions | Treatment policy | This strategy applied as target lesions are the primary focus of RECIST 1.1 evaluations. |
| | Surgical resection of target tumor lesions | Hypothetical | This strategy arises as such events could affect the assessment of a subject's disease status. It is desirable to estimate the treatment effect on PFS without influence of such events. |
| | Receipt of systemic nonprotocol anticancer medications | Hypothetical | |
| | Receipt of local radiation to soft tissue for disease under study | Hypothetical | |
| | Missed two or more consecutive adequate tumor assessments immediately prior to PD or death | Hypothetical | |
| Population summary | Difference in survival functions between treatment conditions as assessed by stratified log-rank test and characterized by the hazard ratio | | |

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[a] See Appendix F for estimand terminology

#### 7.1.1.2. Definition of Progression-Free Survival

For the primary analysis used to characterize the primary estimand (analysis ID PFS-EP-1), duration of PFS is defined as the time from randomization to the earlier of either the date of radiographic progression per BIRC or the date of death due to any cause.

PFS (months) = (earliest date of progression, death, censoring – date of randomization + 1) /30.4375

#### 7.1.1.3. Hypothesis

The hypotheses to be evaluated in the analysis of the PFS are:

$H_0$: $S(t)_{cabozantinib+atezolizumab} = S(t)_{control}$

$H_A$: $S(t)_{cabozantinib+atezolizumab} \neq S(t)_{control}$

where $S(t)_{cabozantinib+atezolizumab}$ and $S(t)_{control}$ are the survival functions for PFS for the experimental and control arms, respectively.

#### 7.1.1.4. Conventions for Analysis

Only ATAs will be considered in the determination of radiographic progression and censoring dates. For the purpose of this study, an ATA is defined as one that results in a time point assignment of complete response, partial response, stable disease/(non-CR, non-PD), or progressive disease or not applicable (NA). NA is assigned when a subject does not have any evidence of measurable or non-measurable disease.

The recorded date of radiographic progression is the date of the tumor assessment visit at which progression is declared. If multiple scan dates are associated with a tumor assessment visit, the earliest scan date within the set will be chosen as the progression date. If a subject has not progressed and multiple scan dates are associated with a tumor assessment visit, the latest scan date within the set will be chosen as the censoring date.

General censoring rules for the primary analysis of PFS are provided in Table 7 (analysis ID PFS-EP-1).

#### 7.1.1.5. Primary Analysis

The timing of this analysis is event-driven and is planned to be conducted after at least 202 events have been observed in the PITT Population (the first 400 randomized subjects). To maintain study equipoise, this analysis will not be conducted before enrollment of approximately 580 subjects is completed (at the time this SAP amendment was written, enrollment had finished on 28 June 2023, with 575 subjects randomized in total). It is designed to include progression events as determined by the BIRC per RECIST 1.1 or death, whichever occurs earlier. Clinical deterioration determined by the Investigator will not be considered as progression events. If more than 202 events are included in the data cutoff for the first 400 randomized subjects, the primary analysis of PFS will include all events; supportive analysis including only the first 202 PFS events in this population will also be provided (Note: in the case that multiple events occur on

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the same date and all of them could be counted as the 202nd event, all these events occurred on the same date will be included in the analysis). An additional supportive analysis of all PFS events in the first 300 randomized subjects (original PITT Population) through the data cutoff will be performed.

The hypothesis testing between experimental arm (cabozantinib + atezolizumab) compared to the control arm (second NHT) will be performed using the stratified log-rank test with a 2-sided $\alpha$=0.002 level of significance. The stratification factors are as described in Section 2.5 and the values used for analysis will be those recorded in the IRT.

The median duration of PFS along with the associated 95% CI for each study treatment arm will be estimated using the Kaplan-Meier method. The stratified HR and its 99.8% and 95% CI will be estimated using a Cox proportional-hazard model with treatment group as the independent variable using the same stratification factors as were used for the log-rank test.

If the p-value for the stratified log-rank test is less than the critical value for rejecting the null hypothesis and the HR ($\lambda_{\text{cabozantinib + atezolizumab}}/\lambda_{\text{control}}$) is < 1, the null hypothesis of no difference between the two study treatment arms will be rejected and it will be inferred that duration of PFS is greater in the experimental arm (cabozantinib + atezolizumab) compared to the control arm.

#### 7.1.1.6. Sensitivity Analyses

All sensitivity analyses will include all subjects in the PITT Population. Tabulated summaries of survival times, HRs, and log-rank test statistics as well as graphs of survival functions will be presented.

The 2 sensitivity analyses (PFS-EP-2 and PFS-EP-3) to support the primary PFS analysis (PFS-EP-1) are shown in Table 7. The 2 sensitivity analyses evaluate the impact of different assumptions or conditions that potentially influence the estimate of the primary estimand:

- The PFS-EP-2 definition evaluates the influence of potentially inconsistent tumor assessment intervals between arms. For subjects who experience radiographic progression, it assigns the date of the scheduled visit as the event date, rather than the date of recorded progression.
- The PFS-EP-3 definition evaluates the influence of the assessor of radiographic progression and is based upon RECIST 1.1 evaluations by the Investigator rather than the BIRC. This definition is used to assess the additional endpoint PFS per RECIST 1.1 as assessed by the Investigator.

The unstratified PFS analysis will also be conducted.

**Table 7: Event and Censoring Rules for Primary and Sensitivity Analyses**

| **Estimand** | Primary | Primary | Primary |
|---|---|---|---|
| **Analysis type** | Primary | Sensitivity | Sensitivity |
| **Analysis purpose** | Primary | Evaluate assessment time bias | Evaluate assessor bias |
| **Analysis ID** | PFS-EP-1 | PFS-EP-2 | PFS-EP-3 |
| **Analysis name** | rPFS per BIRC | Uniform dates | rPFS per Investigator |

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| Estimand endpoint | Radiographic PD | | Radiographic PD | | Radiographic PD | |
|---|---|---|---|---|---|---|
| Population | PITT | | PITT | | PITT | |
| Situation | Outcome | Date of Outcome | Outcome | Date of Outcome | Outcome | Date of Outcome |
| Radiographic PD per RECIST 1.1 per BIRC | event | date of recorded PD | event | date of scheduled visit (or next scheduled visit if between visits) | NA | NA |
| Radiographic PD per RECIST 1.1 per Investigator | NA | NA | NA | NA | event | date of recorded PD |
| Death | event | date of death | event | date of death | event | date of death |
| | Intercurrent events (excluding those with Treatment Policy and principal stratum strategy for all estimands) | | | | | |
| Start of Ukraine war on 24 February 2022 for Ukraine subjects only | NA | NA | NA | NA | NA | NA |
| Clinical deterioration | NA | NA | NA | NA | NA | NA |
| Systemic NPACT (medications) | censored | date of last ATA* before first initiation of therapy | censored | date of last ATA* before first initiation of therapy | censored | date of last ATA* before first initiation of therapy |
| Local NPACT (medications) | NA | NA | NA | NA | NA | NA |
| Surgical resection of target tumor lesion(s) | censored | date of last ATA* before target lesion resection | censored | date of last ATA* before target lesion resection | censored | date of last ATA* before target lesion resection |
| Local radiation: to soft tissue for disease under study | censored | date of last ATA* before local radiation to soft tissue | censored | date of last ATA* before local radiation to soft tissue | censored | date of last ATA* before local radiation to soft tissue |
| | Missing data | | | | | |
| No baseline ATA | censored | date of rand. | censored | date of rand. | censored | date of rand. |
| ≥ 2 consecutive missing scheduled ATA immediately prior to PD or death | censored | date of last ATA* before missing visits | censored | date of last ATA* before missing visits | censored | date of last ATA* before missing visits |
| | Observation ongoing | | | | | |
| None of the above | censored | date of last ATA* | censored | date of last ATA* | censored | date of last ATA* |

ATA = adequate tumor assessment; BIRC = Blinded Independent Review Committee; ITT = intent-to-treat; NA = not applicable; PD = progressive disease; NPACT = nonprotocol anticancer therapy (medications including

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radiopharmaceuticals but excluding local radiation); rPFS = radiographic progression-free survival per RECIST 1.1 per BIRC.
For convention for date of recorded PD, see Section 7.1.1.4.
* or date of randomization if no post-randomization ATA
Blue cells indicate changes from primary analysis.

### 7.1.1.7. Alternative Estimands

Four alternative estimands for PFS arising from changes in strategy for handling some intercurrent events are as defined below:

- Alternative estimand 1 changes the strategy for selected clinical intercurrent events to "composite," resulting in an endpoint that includes as events earlier of either radiographic progression per BIRC, clinical deterioration, receipt of systemic nonprotocol anticancer medications, receipt of radiation therapy to soft tissue for disease under consideration or surgical resection of target tumor lesions or death.
- Alternative estimand 2 changes the strategy to "composite" only for systemic non-protocol anticancer medications, yielding an endpoint that includes as events earlier of either radiographic progression (as well as death) or initiation of systemic NPACT.
- Alternative estimand 3 changes the strategy to "composite" for systemic nonprotocol anticancer medications and missed 2 or more consecutive tumor assessments immediately prior to PD or death, yielding an endpoint that includes radiographic progression as well as death or missed tumor assessments or initiation of systemic NPACT.
- Alternative estimand 4 changes the strategy to "composite" only for missed 2 or more consecutive tumor assessments immediately prior to PD or death, yielding an endpoint that includes radiographic progression as well as death or missed tumor assessments.
- Alternative estimand 5 changes the strategy for the Ukraine war from treatment policy to hypothetical and censoring at the start of the war, yielding an endpoint that includes radiographic progression as well as death until the start of the war for Ukraine subjects.
- Alternative estimand 6 changes the strategy for the Ukraine war from treatment policy to principle stratum and exclusion of all data on all 24 randomized Ukraine subjects. The rational for excluding all 24 randomized Ukraine subjects regardless of PD or deaths that occurred prior to the war or after the start of war is due to the consideration that war impact is multifaceted and data points collected before war and after war initiation were impacted.

More details are provided in Table 8.

**Table 8: Alternative Estimands**

| Estimand Attribute[a] | Event | Alternative 1 Definition | Alternative 2 Definition | Alternative 3 Definition | Alternative 4 Definition | Alternative 5 Definition | Alternative 6 Definition |
|---|---|---|---|---|---|---|---|
| Population | – | Subjects randomized into the study intended to include subjects with mCRPC who have previously received one and only one NHT. | | | | | |
| Endpoint | – | Duration of radiographic and clinical | Duration of radiographic progression or | Evaluate potentially informative | Evaluate potentially informative | Evaluate potentially informative | Evaluate potential multifaceted |

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| Estimand Attribute[a] | Event | Alternative 1 Definition | Alternative 2 Definition | Alternative 3 Definition | Alternative 4 Definition | Alternative 5 Definition | Alternative 6 Definition |
|---|---|---|---|---|---|---|---|
| | | progression-free survival | initiation of systemic NPACT | censoring: Duration of radiographic progression or missed 2 ATAs or initiation of systemic NPACT | censoring: Duration of radiographic progression or missed 2 ATAs | censoring: Duration of radiographic progression due to the start of Ukraine war | impact of War on all 24 randomized Ukraine subjects: Duration of radiographic progression on non-Ukraine subjects |
| Intercurrent events | – | **Strategy** | **Strategy** | **Strategy** | **Strategy** | **Strategy** | **Strategy** |
| | Start of Ukraine war on 24 February 2022 for Ukraine subjects only | Treatment policy | Treatment policy | Treatment policy | Treatment policy | hypothetical | Principle stratum |
| | Receipt of non-assigned study treatment, dose reduction and delay/ interruption, and treatment discontinuation | Treatment policy | Treatment policy | Treatment policy | Treatment policy | Treatment policy | Treatment policy |
| | Clinical deterioration | Composite | Treatment policy | Treatment policy | Treatment policy | Treatment policy | Treatment policy |
| | Receipt of local radiation to bone | Treatment policy | Treatment policy | Treatment policy | Treatment policy | Treatment policy | Treatment policy |
| | Surgical resection of non-target tumor lesions | Treatment policy | Treatment policy | Treatment policy | Treatment policy | Treatment policy | Treatment policy |
| | Surgical resection of target tumor lesions | Composite | Hypothetical | Hypothetical | Hypothetical | Hypothetical | Hypothetical |
| | Receipt of systemic nonprotocol anticancer | Composite | Composite | Composite | Hypothetical | Hypothetical | Hypothetical |

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| Estimand Attribute[a] | Event | Alternative 1 Definition | Alternative 2 Definition | Alternative 3 Definition | Alternative 4 Definition | Alternative 5 Definition | Alternative 6 Definition |
|---|---|---|---|---|---|---|---|
| | medications | | | | | | |
| | Receipt of local radiation to soft tissue for disease under study | Composite | Hypothetical | Hypothetical | Hypothetical | Hypothetical | Hypothetical |
| Missing data | Missed two or more consecutive adequate tumor assessments immediately prior to PD or death | Hypothetical | Hypothetical | Composite | Composite | Hypothetical | Hypothetical |
| Population summary | Difference in survival functions between treatment conditions as assessed by stratified log-rank test and characterized by the hazard ratio. | | | | | | |

Shaded cells differ from primary estimand.
[a] See Appendix F for estimand terminology.

### 7.1.1.8. Supplemental Analyses

Event and censoring definitions are provided in Table 9 for five supplemental analyses PFS-EA1, PFS-EA2, PFS-EA3, PFS-EA4, PFS-EA5, and PFS-EA6 corresponding to alternate estimands PFS-EA1, PFS-EA2, PFS-EA3, PFS-EA4, PFS-EA5, and PFS-EA6 for PFS respectively.

**Table 9: Event and Censoring Rules for Supplementary Analyses of Alternative Progression-Free Survival Estimands**

| Estimand | Alternative 1 | Alternative 2 | Alternative 3 | Alternate 4 | Alternate 5 | Alternate 6 |
|---|---|---|---|---|---|---|
| **Analysis type** | Supplementary | Supplementary | Supplementary | Supplementary | Supplementary | Supplementary |
| **Analysis purpose** | Alternate progression definition | Alternate progression definition | Evaluate potentially informative censoring | Evaluate potentially informative censoring | Evaluate potentially informative censoring | Evaluate potential multifaceted impact of War on all data for all 24 randomized Ukraine subjects. |
| **Analysis ID** | PFS-EA1 | PFS-EA2 | PFS-EA3 | PFS-EA4 | PFS-EA5 | PFS-EA6 |

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| **Analysis name** | Investigator claims | | rPFS or sNPACT | | rPFS or sNPACT or missing ATA | | rPFS or missing ATA | | rPFS censoring at the start of the Ukraine war | | rPFS excluding all data for all 24 Ukraine subjects randomized | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Estimand endpoint** | Radiographic or clinical PD | | Radiographic PD or initiation of systemic NPACT | | Radiographic PD ore missed 2 ATAs or initiation of systemic NPACT | | Radiographic PD or missed 2 ATAs | | Radiographic PD censoring at the start of the Ukraine war | | Radiographic PD excluding all data on all 24 Ukraine subjects randomized | |
| **Population** | PITT | | PITT | | PITT | | PITT | | PITT | | PITT excluding Ukraine subjects | |
| **Situation** | **Outcome** | **Date of Outcome** | **Outcome** | **Date of Outcome** | **Outcome** | **Date of Outcome** | **Outcome** | **Date of Outcome** | **Outcome** | **Date of Outcome** | **Outcome** | **Date of Outcome** |
| Radiographic PD per RECIST 1.1 per BIRC | NA | NA | event | date of recorded PD | event | date of recorded PD | event | date of recorded PD | event | date of recorded PD | event | date of recorded PD |
| Radiographic PD per RECIST 1.1 per Investigator | event | date of recorded PD | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Death | event | date of death | event | date of death | event | date of death | event | date of death | event | date of death | event | date of death |
| Intercurrent events (excluding those with Treatment Policy or Principal Stratum strategy for all estimands) | | | | | | | | | | | | |
| Start of Ukraine war on 24 February 2022 for Ukraine subjects only | NA | NA | NA | NA | NA | NA | NA | NA | censored | date of last ATA* before the start of war | NA (excluding Ukraine subjects) | NA (excluding Ukraine subjects) |
| Clinical deterioration | event | date of determination of clinical deterioration | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |

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| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Systemic NPACT (medications) | event | date of first initiation of therapy | event | date of first initiation of therapy | event | date of first initiation of therapy | censored | Date of last ATA before systemic NPACT | censored | Date of last ATA before systemic NPACT | censored | Date of last ATA before systemic NPACT |
| Local NPACT (medications) | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Surgical resection of target tumor lesion(s) | event | date of target lesion resection | censored | date of last ATA* before target lesion resection | censored | date of last ATA* before target lesion resection | censored | date of last ATA* before target lesion resection | censored | date of last ATA* before target lesion resection | censored | date of last ATA* before target lesion resection |
| Local radiation: to soft tissue for disease under study | event | date of local radiation | censored | date of last ATA* before local radiation | censored | date of last ATA* before of local radiation | censored | date of last ATA* before of local radiation | censored | date of last ATA* before of local radiation | censored | date of last ATA* before of local radiation |
| | Missing data | | | | | | | | | | | |
| No baseline ATA | censored | date of rand. | censored | date of rand. | censored | date of rand. | censored | date of rand. | censored | date of rand. | censored | date of rand. |
| ≥ 2 consecutive missing scheduled ATA immediately prior to PD or death | censored | date of last ATA* before missing visits | censored | date of last ATA* before missing visits | Event | date of last ATA* before missing visits | Event | date of last ATA* before missing visits | censored | date of last ATA* before missing visits | censored | date of last ATA* before missing visits |
| **Situation** | **Outcome** | **Date of Outcome** | **Outcome** | **Date of Outcome** | **Outcome** | **Date of Outcome** | **Outcome** | **Date of Outcome** | **Outcome** | **Date of Outcome** | **Outcome** | **Date of Outcome** |
| | Observation ongoing | | | | | | | | | | | |
| None of the above criteria for event or censoring | censored | date of last ATA* | censored | date of last ATA* | censored | date of last ATA* | censored | date of last ATA* | censored | date of last ATA* | censored | date of last ATA* |

ATA = adequate tumor assessment; BIRC = Blinded Independent Review Committee; ITT = intent-to-treat; NA = not applicable; PD = progressive disease; NPACT = nonprotocol anticancer therapy (medications including radiopharmaceuticals but excluding local radiation).

For convention for date of recorded PD, see Section 7.1.1.4.

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* or date of randomization if no post-randomization ATA.
Blue cells indicate changes from primary analysis.

#### 7.1.1.9. Exploratory Analyses

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

### 7.1.2. Duration of Overall Survival

#### 7.1.2.1. Primary Estimand

The primary estimand for OS is the difference in survival functions between treatment conditions in the duration of OS in the targeted patient population, irrespective of the start of the Ukraine War for Ukraine subjects, irrespective of whether the assigned study treatment was given, and irrespective of whether nonprotocol anticancer therapy or radiation of any kind was given.

Estimand definition and rationale are presented in Table 10.

**Table 10: Estimand Definition and Rationale for Primary Estimand**

| **Estimand Attribute[a]** | **Primary Definition** | | **Rationale (As Needed)** |
|---|---|---|---|
| Population | Subjects randomized into the study intended to include subjects with mCRPC who have previously received one and only one NHT. | | The initial clause "Subjects randomized into the study intended to include…" is included to align the estimand with the application of the ITT principle expected by regulatory reviewers |
| Endpoint | Duration of overall survival | | |
| Intercurrent event(s) | **Event** | **Strategy** | **Rationale (as needed)** |
| | Start of Ukraine war on 24 February 2022 for Ukraine subjects only | Treatment policy | This strategy applied to align the estimand with the application of the ITT principle expected by regulatory reviewers |
| | Receipt of non-assigned study treatment or non-receipt of study treatment | Treatment policy | This strategy applied to align the estimand with the application of the ITT principle expected by regulatory reviewers |
| | Receipt of nonprotocol anticancer therapy or radiation of any kind | Treatment policy | |
| | Lost to follow- up | Hypothetical | This strategy arises as a consequence of the convention of censoring at loss to follow up and the assumption in the Kaplan-Meier model that censored subjects would have behaved in a fashion similar to those not censored, ie, not experienced these intercurrent event(s) |

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| Estimand Attribute[a] | Primary Definition | Rationale (As Needed) |
|---|---|---|
| Population summary | Difference in survival functions between treatment conditions | |

[a] See Appendix F for estimand terminology.

#### 7.1.2.2. Definition of Overall Survival

For the primary analysis directed toward the primary estimand (analysis ID OS-EP-1), duration of OS is defined as the time from randomization to death due to any cause. For subjects who are not known to have died at the time of data cutoff and are permanently lost to follow up, duration of OS will be right censored at the earlier of the following dates: date the subject was last known to be alive or date of full withdrawal of consent (including survival follow up), or date of data cutoff.

OS (months) = (earlier of date of death or censoring – date of randomization + 1)/30.4375

#### 7.1.2.3. Hypothesis

The hypotheses to be evaluated in the analysis of the OS are:

$$H_0: S(t)_{cabozantinib+atezolizumab} = S(t)_{control}$$

$$H_A: S(t)_{cabozantinib+atezolizumab} \neq S(t)_{control}$$

where $S(t)_{cabozantinib+atezolizumab}$ and $S(t)_{control}$ are the survivor functions for OS for the experimental and control arms, respectively.

#### 7.1.2.4. Primary Analysis

The timing of this analysis is event-driven, and it will be conducted after at least 340 deaths (OS events) have been observed in the experimental and control arms in the ITT Population. The actual number of events at the time of analysis may be higher than 340 due to the logistics of estimating event counts in an ongoing multicenter clinical study and predicting cutoff dates for analysis.

The hypothesis testing between the experimental arm (cabozantinib + atezolizumab) compared to the control arm will be performed using a 2-sided stratified log-rank test. See Section 7.2 for details regarding the allocation of overall Type I error (α-level). The stratification factors are as described in Section 2.5 and the values used for analysis will be those recorded in the IRT.

Additionally, up to 2 interim analyses of OS are planned at approximately the 45% and 76% information fractions. The critical p-values (and observed HRs) for testing these interim hypotheses will be based on Lan-DeMets O'Brien-Fleming alpha-spending function. The overall α to be spent on testing the duration of OS via the use of a spending function will as described in Section 7.2. The actual critical values for each OS analysis will depend upon the true number of events observed at conduct of each analysis. Interim analyses details are provided in Section 7.3.

The median duration of OS along with the associated 95% CI for each study treatment arm will be estimated using the Kaplan-Meier method. The stratified HR along with the associated (1-α)%

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and 95% CIs will be estimated using a Cox proportional-hazard model with treatment group as the independent variable using the same stratification factors as were used for the log-rank test.

If at any OS analysis (interim or primary) the p-value for the stratified log-rank test is less than the critical value for rejecting the null hypothesis and the HR ($\lambda_{\text{cabozantinib + atezolizumab}}/\lambda_{\text{control}}$) is < 1, the null hypothesis of no difference between the 2 study treatment arms will be rejected and it will be inferred that duration of OS is greater in the experimental arm (cabozantinib + atezolizumab) compared with the control arm.

The unstratified versions of all the above analyses will also be conducted.

#### 7.1.2.5. Alternative Estimand

One alternative estimand for OS arising from changes in strategy for handling some intercurrent events to "hypothetical" is defined in Table 11. This analysis is intended to "factor out" the effects of nonprotocol anticancer therapy on OS, in the targeted patient population, irrespective of whether the assigned study treatment was given.

Another alternative estimand for OS is the difference in survival functions between treatment conditions in the duration of OS in the targeted patient population, censoring Ukraine subject data at the start of the war using a hypothetical estimand approach, irrespective of whether the assigned study treatment was given, and irrespective of whether nonprotocol anticancer therapy or radiation of any kind was given. (Table 11). Shaded cells differ from primary estimand. The third alternative estimand for OS is difference in survival functions between treatment conditions in the duration of OS in the targeted patient population, excluding all data on all 24 randomized Ukraine subjects using principle estimand approach, irrespective of whether the assigned study treatment was given, and irrespective of whether nonprotocol anticancer therapy or radiation of any kind was given. (Table 11). Shaded cells differ from primary estimand.

**Table 11: Estimand Definition and Rationale for Alternative Estimand**

| **Estimand Attribute**[a] | | **Alternate definition 1** | **Alternate definition 2** | **Alternate definition 3** |
|---|---|---|---|---|
| Population | Subjects randomized into the study intended to include subjects with mCRPC who have previously received one and only one NHT | | | |
| Endpoint | Duration of overall survival | | | |
| | **Event** | **Strategy** | **Strategy** | **Strategy** |

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| Estimand Attribute[a] | | Alternate definition 1 | Alternate definition 2 | Alternate definition 3 |
|---|---|---|---|---|
| Intercurrent event(s) | Start of Ukraine war on 24 February 2022 for Ukraine subjects only | Treatment policy | Hypothetical | Principle Stratum |
| | Receipt of non-assigned study treatment or non-receipt of study treatment | Treatment policy | Treatment policy | Treatment policy |
| | Receipt of systemic nonprotocol anticancer therapy | Hypothetical | Treatment policy | Treatment policy |
| | Receipt of radiation of any kind | Treatment policy | Treatment policy | Treatment policy |
| | Lost to follow up | Hypothetical | Hypothetical | Hypothetical |
| Population summary | Difference in survival functions between treatment conditions | | | |

[a] See Appendix F for estimand terminology

#### 7.1.2.6. Supplemental Analyses

A supplemental analysis (OS-EA1) directed at the alternative estimand will be conducted in the experimental and control arms in the ITT Population. In this analysis a subject receiving non-protocol systemic will be right censored at the first start date of such subsequent anticancer therapy. Summaries will be provided as for the primary analysis of OS.

A supplemental analysis (OS-EA2) directed at the alternative estimand will be conducted in the experimental and control arms in the ITT Population, censoring at the start of the war for Ukraine subjects (using a hypothetical estimand approach). Summaries will be provided as for the primary analysis of OS.

A supplemental analysis (OS-EA3) directed at the alternative estimand will be conducted in the experimental and control arms in the ITT Population, excluding all data on all 24 randomized Ukraine subjects (using principle stratum estimand approach). Summaries will be provided as for the primary analysis of OS.

#### 7.1.2.7. Exploratory Analyses

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

## 7.2. Control of Type I Error

Inflation of Type 1 error associated with testing of multiple primary endpoints will be controlled by a closed testing procedure that employs modified Bonferroni and fallback methods. The study-wise 2-sided alpha of 0.05 will be nominally divided between multiple primary endpoints

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PFS (0.002) and OS (0.048) with prespecified alpha levels passed from significant endpoints to those to be tested next per the prespecified testing strategy.

Two interim analyses of OS are planned. Inflation of Type 1 error associated with interim analyses will be controlled using a Lan-DeMets O'Brien-Fleming (LD-OF) alpha-spending function.

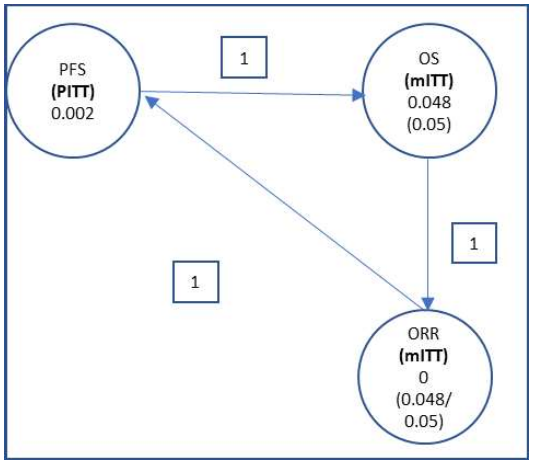
Inflation of Type 1 error associated with testing the secondary endpoint of ORR will be controlled by applying a hierarchical testing procedure. ORR will only be tested if the null hypothesis for OS is rejected in favor of the experimental arm (cabozantinib + atezolizumab).

Testing and alpha reallocation will proceed as follows:

At the primary PFS analysis, test PFS at 0.002 level. Then:

1. If PFS is significant, re-allocate 0.002 alpha to OS and conduct the planned interim and final analyses of OS per LD-OF at 0.05 allocated alpha
    a. If OS is not significant at any analysis, procedure ends
    b. If OS is significant at any analysis, re-allocate its 0.05 alpha to ORR and test ORR at 0.05 in the ORR analysis population at the later of OS IA1 data cutoff or when all enrolled subjects have had a chance to be followed for 6 months
2. If PFS is not significant, conduct the planned interim and final analyses of OS per LD-OF at 0.048 allocated alpha
    a. If OS is not significant at any analysis, procedure ends
    b. If OS is significant at any analysis, re-allocate its 0.048 alpha to ORR and test ORR at 0.048 in the ORR analysis population at the later of OS IA1 data cutoff or when all enrolled subjects have had a chance to be followed for 6 months
        i. If ORR is significant at 0.048, retest PFS at 0.05
        ii. If ORR is not significant at 0.048, procedure ends

The allocation described above is as follows:




All other statistical evaluations of efficacy will be considered exploratory.

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## 7.3. Interim Analyses

The number of events required to evaluate OS is based upon assumptions currently available and provides high power to detect the smallest clinically meaningful difference in OS under these assumptions. However, as there is uncertainty in the assumptions, interim analyses provide an opportunity to stop the study early if the treatment benefit of the experimental arm is larger than expected, potentially allowing the new regimen to become available sooner to this patient population.

Two interim analyses of OS are planned and will include all subjects randomized to combination and second NHT control arms at the time of each analysis. The first interim analysis of OS will be conducted at the time of primary analysis of PFS. Based on the updated enrollment rate, this is expected to occur at approximately the 45% information fraction for OS. The second interim analysis of OS is planned at approximately the 76% information fraction. Inflation of Type 1 error associated with these interim analyses will be controlled using LD-OF alpha-spending functions based upon a total alpha allocation for OS that depends upon whether the PFS result is significant.

Details and boundaries for testing OS at interim and the final analyses are shown in Table 12.

**Table 12: Details and Boundaries for the Interim and Final Analyses of Overall Survival**

| OS Alpha | | | PFS Is Significant 0.05 | | PFS Is Not Significant 0.048 | |
|---|---|---|---|---|---|---|
| **OS analysis information fraction** | **Approximate # of events** | **Analysis Time** | **Critical p-value** | **Max HR to reject** | **Critical p-value** | **Max HR to reject** |
| 45% | 153 | 27 | 0.002 | 0.601 | 0.002 | 0.599 |
| 76% | 258 | 35 | 0.020 | 0.748 | 0.019 | 0.746 |
| 100% | 340 | 44 | 0.044 | 0.803 | 0.042 | 0.802 |

HR = hazard ratio; OS = overall survival; PFS = progression-free survival.

Due to logistical considerations in event ascertainment and operational planning and conduct, the actual analyses may include more or fewer events than the target information fractions. The actual critical values employed at the interim and final analyses of OS will depend upon the actual information fraction at the time of the analyses.

Should the timing of the first interim analysis of OS (IA1) transpire at an information fraction much higher than expected (eg, due to faster-than-expected deaths or slower-than expected PFS events), the interim analyses of OS will be conducted as specified in Table 13.

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**Table 13: Interim Analysis Strategy for Overall Survival**

| OS IA1 IF | Proceed as | Rationale |
|---|---|---|
| < 50% | Perform IA1 and IA2 as planned | Similar conditions to original plan |
| 50 to < 65% | • perform IA1 at time of primary PFS<br>• Conduct IA2 at 80% IF | • Higher than expected information for OS negates administrative nature of the analysis<br>• Preserves two IA as planned with reasonable intervals between them |
| ≥ 65% | perform a single IA of OS at the time of primary PFS | With higher than 65% IF, it is reasonable for OS IA. Doing multiple data cuts might not be logistically preferred |

IA = Interim Analysis; PFS = progression-free survival; OS = overall survival.

If the null hypothesis of no differences in OS is rejected at the planned interim OS analysis in favor of the arm with cabozantinib + atezolizumab, no subsequent testing of OS is planned.

Interim analysis of PFS and futility analyses of PFS or OS are not planned.

## 7.4. Secondary Efficacy Endpoint

### 7.4.1. Objective Response Rate - Blinded Independent Review Committee

For each subject, best overall response (BOR) is defined as the best tumor assessment category as determined per RECIST 1.1 by BIRC that occurs through the first overall time point response of PD, and prior to any of the censoring events defined for the primary analysis of PFS as described in Section 7.1.1. Tumor assessment categories are ranked as: confirmed CR, confirmed PR, SD, PD, and not evaluable (NE). To be classified as confirmed CR or confirmed PR, confirmation must have occurred on a subsequent visit that is ≥ 28 days after the response was first observed. To be classified as SD, at least one timepoint response of SD must be documented ≥ 42 days after randomization. The ORR is defined as the proportion of subjects with a BOR of confirmed CR or confirmed PR. Subjects without post-baseline tumor assessments will be counted as non-responders.

ORR will be tested using the Cochran-Mantel-Haenszel test (stratified by the randomization stratification factors) at the 2-sided α level (the α level as defined in Section 7.2) in the ITT Population with measurable disease at baseline, provided the null hypothesis for OS is rejected in favor of the experimental arm (cabozantinib + atezolizumab) at the interim or final analysis. Point estimates of ORR and associated 95% confidence interval estimates calculated by exact methods will be provided. The 2-sided CIs for the difference in ORR between the 2 study treatment arms and for the odds ratio will be calculated using asymptotic methods.

Waterfall plots displaying maximum percent tumor reduction since baseline in target lesions will be generated for tumor assessment data per BIRC.

These plots will include subjects with a tumor assessment at baseline and at least 1 post-baseline visit. For each subject, data on or after the progression/censoring date described in PFS-EP-1 analysis Section 7.1.1 will be excluded from the waterfall plots.

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One sensitivity analysis will be performed similarly by excluding all 24 randomized Ukraine subjects. Another sensitivity analysis will be performed on assessments through the first overall time point response of PD and prior to any of the censoring events defined for the PFS-EA5 as described in Section 7.1.1.8.

A summary of concordance between the BIRC and Investigator determinations of objective response status and dates will also be provided.

## 7.5. Additional Endpoints

Each exploratory endpoint will be analyzed using an appropriate two-sided statistical test without adjustment for multiplicity unless specified otherwise. Statistical results for exploratory endpoints will be considered supportive. Exploratory analyses will be performed on the ITT Population unless specified otherwise.

### 7.5.1. PSA Response Rate

PSA response is defined as a ≥ 50% decline in PSA from baseline confirmed by a repeat measurement at least 21 days later. Point estimates of PSA response rate for each study treatment arm, the difference in PSA response rate between the study treatment arms and associated 95% CIs will be provided. The odds ratio and associated 95% CIs will also be presented. The 2-sided CIs for the point estimate will be calculated using exact methods. The 2-sided CIs for the difference in PSA response rate between the two study treatment arms and for the odds ratio will be calculated using asymptotic methods. All summaries for PSA response rate will be provided for the ITT Population. Waterfall plots displaying maximum percent reduction in PSA since baseline will be generated.

### 7.5.2. Duration of Objective Response

Duration of objective response is defined as the time from the first documentation of objective response that is subsequently confirmed at a visit that is ≥ 28 days later to disease progression or death due to any cause.

Duration of response (months) = (earliest date of progressive disease or death due to any cause or censoring – date of first objective response + 1)/30.4375

DOR will be computed only among subjects who experience an objective response (confirmed CR or confirmed PR). DOR will be analyzed and presented separately per BIRC and per Investigator for subjects in the ITT Populations. For DOR per BIRC and per Investigator, the dates of progression and censoring are shown in column PFS-EP-1per BIRC and PFS-EP-3 per Investigator in Table 7, respectively.

DOR will be analyzed using the Kaplan-Meier method.

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### 7.5.3. Progression-Free Survival Per Prostate Cancer Working Group 3

PFS by PCWG3 criteria per BIRC defined as the time from randomization to the earlier of either radiographic PD based on CT/MRI per RECIST 1.1 per BIRC or bone disease progression based on bone scans per PCWG3 per BIRC or death due to any cause. The analysis and censoring rule for PFS by PCWG3 will be similar to PFS-EP-1 by RECIST 1.1. In addition to other censoring rules for primary PFS-EP-1by RECIST 1.1, subjects who had any nonprotocol radiation therapy to bone will be right censored at the date of the last tumor assessment prior to the date of initiation of nonprotocol radiation therapy to bone.

### 7.5.4. Time to Prostate-Specific Antigen Progression

PSA progression is defined as an increase of 2 μg/L and ≥ 25% increase from nadir confirmed by subsequent rising PSA at least 21 days later. Time to PSA progression is the time from date randomization to first date of PSA progression. Time to PSA progression will be analyzed using the Kaplan-Meier method. Subjects who receive systemic NPACT will be censored at the last PSA assessment prior to the date of initiation of subsequent therapy.

PSA progression (months) = (earliest date of progression [increase of 2 μg/L and ≥ 25% increase from nadir confirmed by subsequent rising PSA at least 21 days later], censoring – date of randomization + 1)/30.4375.

### 7.5.5. Time to Symptomatic Skeletal Events

Symptomatic skeletal events (SKEs) will be continuously assessed from RSV1 through the FU-2 Visit. Time to SSE is defined as time from randomization to earliest of any one of the following:

- Radiation therapy to bone,
- Surgery to bone,
- Spinal cord compression, or
- Symptomatic fracture.

Time to SSE will be analyzed using the Kaplan-Meier method. Subjects who receive systemic NPACT will be censored at the last skeletal assessment prior to the date of initiation of subsequent therapy.

Time to SSE (months) = (earliest date of progression [radiation therapy to bone; surgery to bone; spinal cord compression; symptomatic fracture], censoring – date of randomization + 1)/30.4375.

### 7.5.6. Time to Pain Progression

Time to pain progression is defined as time from randomization to earliest of:

- ≥ 2-point increase in pain score compared to baseline in 11-point numeric rating scale (NRS) measuring worst pain in the last week
- New or increased analgesic use from baseline (for analgesic taken for at least 7 consecutive days)

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Time to pain progression will be analyzed using the Kaplan-Meier method for subjects in the ITT Population. Subjects who receive systemic NPACT will be censored at the last pain assessment prior to the date of initiation of subsequent therapy.

Time to Pain Progression (months) = (earliest date of progression [≥ 2-point increase in pain or new or increased analgesic use], censoring – date of randomization + 1)/30.4375.

The following summaries are planned at each time point for each treatment arm for subjects in the ITT Population:

- Rate of completion for the pain assessment at each time point. This is defined as the total number of subjects with a pain score / the expected total number of subjects still on study at the visit.
- Descriptive statistics (number of observations, mean and standard deviation (SD), median, Q1 and Q3) of the pain assessment and change from baseline; group differences will be presented as well; mean+/ standard error (SE) plots could be used to display change from baseline until number of expected total number of subjects still on study at the visit drops under 30 in either arm.

### 7.5.7. Time to Chemotherapy

Time to chemotherapy is define as time from randomization to start of chemotherapy. Time to chemotherapy will be analyzed using the Kaplan-Meier method.

Time to Chemotherapy (months) = (earliest date of chemotherapy, censoring – date of randomization + 1)/30.4375.

### 7.5.8. Health Care Resource Utilization

For this study the following health care resource utilization (HCRU) parameters collected during the study observation period will be summarized for subjects in the Safety Population:

- Days of hospitalization due to SAEs
- Days in intensive care unit (ICU) due to SAEs
- Number of emergency room (ER) visits due to SAEs
- Number and type of surgeries
- Number and type of transfusions

The summaries will include:

- Number and percentage of subjects in each category of HCRU
- Descriptive statistics for each HCRU category amongst those subjects who utilized the respective resource
- Total number of days or visits as applicable for each HCRU
- Per person year summary for each HCRU

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To calculate the per person year value for a subject for a HCRU parameter, the numerator is the sum of the days or visits for that subject for the parameter; and the denominator is defined as: (end of safety observation period – date of randomization + 1) / 365.25.

### 7.5.9. Health-Related Quality of Life Assessment

Descriptive statistics of EQ-5D-5L and EORTC QLQ-C30 by visit will be provided. Separately from the CSR, additional HRQOL analyses may be performed and reported. Only assessments before the initiation of systemic nonprotocol anticancer therapy and prior to the end of study treatment will be included in the analysis.

#### 7.5.9.1. EQ-5D-5L

Health-related quality of life (HRQOL) will be assessed by the EuroQol Health questionnaire EQ-5D-5L. The questionnaire will be self-completed by the subjects at various time points regardless of whether study treatment was given, reduced, held, or discontinued until the date of the last tumor imaging assessment or the study completion. Consequently, these assessments may be required in the Post-treatment Period for some subjects (see protocol Section 5.6.8). The EQ-5D-5L questionnaire has 2 pages: a descriptive page which assesses on an increasing severity scale of 1 (no problems with function/no symptoms) through 5 (unable to perform function/extreme symptoms) changes in the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The second page has a 0 through 100 visual analogue scale (VAS) which records the subject's self-rated health between 100 (best health you can imagine) and 0 (worst health you can imagine) and serves as quantitative measure of health by the subject. The digits for each of the five dimensions of the EQ-5D-5L will be combined into a 5-digit health state which will be converted to a single index (EQ-Index) value using the UK value set (see Appendix D). The EQ-Index ranges from states worse than dead (<0) to 1 (full health).

For subjects in the ITT Population, the following summaries are planned at each time point for EQ-5D-5L for each treatment arm:

- Rate of completion for the questionnaire at each time point. This is defined as total number of subjects who answered all 5 dimensions on the EQ-5D-5L questionnaire / the expected total number of subjects still on study at the visit
- The number and percentage will be summarized by each dimension (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and level (level 1 through level 5) for each scheduled timepoint
- The number and percentage of subjects with 'any problems' (levels 2, 3, 4 and 5) will be summarized by each dimension (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) for each scheduled timepoint; group difference will also be presented; graphical displays could be used until number of expected total number of subjects still on study at the visit drops under 30 in either arm
- Descriptive statistics (mean and SD, median, Q1 and Q3) for VAS score, EQ-Index, and change from baseline at each timepoint will be presented; group difference of change from baseline will also be presented; mean+/-SE for VAS score and EQ-Index change

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from baseline will be plotted until number of expected total number of subjects still on study at the visit drops under 30 in either arm

#### 7.5.9.2. EORTC QLQ-C30

HRQOL will also be assessed by the EORTC QLQ-C30 (Version 3.0) which consists of 30 items (ie, single questions). See Appendix E for details. The QLQ-C30 includes 5 functional scales, 3 symptom scales, a global health status / QoL scale, and 6 single items. Each of the multi-item scales includes a different set of items; no item occurs in more than 1 scale. See Table 14 for details on these scales/items.

**Table 14: EORTC QLQ-C30 Scales/Items**

| Global health status / QoL | Scale | Number of items | Item range * | Version 3.0 Item numbers | Function scales |
|---|---|---|---|---|---|
| Global health status / QoL | QL2 | 2 | 6 | 29, 30 | |
| **Functional scales** | | | | | |
| Physical Functioning | PF2 | 5 | 3 | 1 to 5 | F |
| Role Functioning | RF2 | 2 | 3 | 6, 7 | F |
| Emotional functioning | EF | 4 | 3 | 21 to 24 | F |
| Cognitive functioning | CF | 2 | 3 | 20. 25 | F |
| Social functioning | SF | 2 | 3 | 26, 27 | F |
| **Symptom scales / items** | | | | | |
| Fatigue | FA | 3 | 3 | 10, 12, 18 | |
| Nausea and vomiting | NV | 2 | 3 | 14, 15 | |
| Pain | PA | 2 | 3 | 9, 19 | |
| Dyspnoea | DY | 1 | 3 | 8 | |
| Insomnia | SL | 1 | 3 | 11 | |
| Appetite loss | AP | 1 | 3 | 13 | |
| Constipation | CO | 1 | 3 | 16 | |
| Diarrhoea | DI | 1 | 3 | 17 | |
| Financial difficulties | FI | 1 | 3 | 28 | |

*Item range is the difference between the possible maximum and the minimum response to individual items; most items take values 1 to 4, giving range = 3.

The principle for deriving the scales is to first take the average of the items that contribute to the scale (this is the raw score) and then use a linear transformation to standardize the raw score, so that scores range from 0 to 100 (Fayers et al, 2001).

Scores in each scale will be generated if at least half of the items comprising the scale have been answered. For single-item scales with missing responses and scales where less than half of the items have not been answered, scale scores will be set to missing. Scale scores will range from 0 to 100 after linear transformation, with a high scale score representing a higher response level:

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- A high score for a functioning scale represents a high/healthy level of functioning
- A high score for the global health status/QoL represents a high QoL
- A high score for a symptom scale/item represents a high level of symptomatology/problems.

For subjects in the ITT Population, the following summaries are planned at each time point for each treatment arm:

- Rate of completion for the questionnaire at each time point. This is defined as total number of subjects for whom all 15 scales can be obtained / the expected total number of subjects still on study at the visit.
- Descriptive statistics (number of observations, mean and SD, median, Q1 and Q3) of the linearly transformed values and change from baseline for the 15 scales/items; group differences will be presented as well; mean+/SE plots could be used to display change from baseline until number of expected total number of subjects still on study at the visit drops under 30 in either arm.

#### 7.5.9.3. Pharmacokinetics

Descriptive statistics of cabozantinib plasma concentration and atezolizumab serum concentration by planned visit will be provided. The PK component of the CSR will be generated and reported by Exelixis's Clinical Pharmacology & Pharmacometrics group. Separately from the CSR, population PK modeling may be performed and reported.

### 7.5.10. Immunogenicity Assessments

Anti-drug antibody (ADA) in serum will be assessed at baseline prior to first dose administration, and at multiple time points post dose administration during Treatment and Follow-up Phase of the study using validated tiered immunoassay. Neutralizing antibody assay may be applied if deemed necessary. The incidence rate of positive antibodies to atezolizumab will be reported. All valid assay results from subjects who receive treatment will be included in the ADA summaries. The relationship between atezolizumab exposure and the status of ADA may be explored.

### 7.5.11. Correlation of Immune Cell, Tumor Cell, and Plasma Biomarker

The following baseline biomarker subgroups may be explored for primary and secondary efficacy endpoints

- PD-L1 status by SP263

Tumor markers such as PD-L1 will be measured at baseline on tumor specimen samples. PD-L1 status will be assessed by four different scoring methods, including combined positive score (CPS), tumor proportion score (TPS), immune cell area (ICAREA), and visually estimated combined positive score (vCPS). Analysis of PFS, OS, and ORR per RECIST 1.1 by BIRC will be performed by PD-L1 status ($\geq 1\%$, $< 1\%$, Indeterminate) defined by each scoring method.

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## 7.6. Subgroups

The following subgroups based on baseline characteristics and stratification factors as reported by the Investigator on the CRF will be explored for primary and secondary efficacy endpoints.

- Age category
  - < 65 years
  - 65 to < 75 years
  - 75 to < 85 years
  - ≥ 85 years
- Race
  - Asian
  - Black/African American
  - White
  - Other/not reported
- Geographic Regions
  - North America
  - Europe
  - Asia Pacific
  - Latin America
- ECOG Performance status at baseline:
  - 0
  - 1
  - Missing
- Liver metastasis per stratification factors and per CRF:
  - Yes
  - No
- Prior docetaxel per stratification factors and per CRF:
  - Yes
  - No
- First NHT given for per stratification factors and per CRF:
  - metastatic CSPC
  - M0 CRPC

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  - mCRPC

    Note: For subjects who have received the same NHT for both mCRPC and either mCSPC (including locally advanced M0 CSPC) or M0 CRPC, subjects should be stratified by the disease state for which they received their first NHT even if they did not progress on it.

- Gleason score at diagnosis
  - < 8
  - ≥ 8
- Diagnosis with de novo metastatic disease
  - Yes
  - No
- Bone disease
  - Yes
  - No
- PSA progression at baseline:
  - Yes
  - No
- Soft tissue progression at baseline:
  - Yes
  - No
- Disease location at baseline:
    - Measurable extrapelvic visceral disease only
    - Measurable extrapelvic adenopathy only
    - Both
    - None

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# 8. SAFETY SUMMARIES

All safety analyses will be performed on data as described in Section 4.6 for subjects in the Safety Population. A few summaries may be generated on the P-Safety Population and the 24 Ukraine subjects separately. No formal statistical comparison between the experimental and control arms is planned.

Safety and tolerability will be assessed by the incidence of treatment-emergent adverse events (TEAEs), changes in laboratory parameters and vital signs from baseline, and ECOG PS.

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

The primary responsibility of the IDMC is to review the accumulating safety data on a regular and ad hoc basis and make recommendation to the Sponsor regarding the continued conduct of the study. Safety data will be provided at regular intervals to the IDMC in the form of summary reports or data listings from the Sponsor or its designated representative.

Details regarding IDMC membership, schedule and format of meetings, format for presentation of data, access to interim data, mode and timing of providing interim reports to the IDMC, and other issues relevant to committee operations are described in the IDMC charter.

The IDMC members will use their expertise, experience, and judgment to evaluate the safety data from the study and recommend to the Sponsor whether the study should continue or be stopped early for safety. No formal statistical rules recommending early stopping for safety are planned.

## 8.1. Adverse Events

Adverse event (AE) terms recorded on the CRF will be mapped to preferred terms and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA). The severity of AEs will be measured by National Cancer Institute (NCI) CTCAE v5.0 (Common terminology criteria for adverse events) guidelines. The Investigator will judge each event to be “not related” or “related” to study treatment. For subjects in the experimental arm, the Investigator will judge each event’s relationship to study treatment, separately for cabozantinib and atezolizumab. However, in summarizing relationship of study treatment to AEs in the experimental arm, relationship to either cabozantinib or atezolizumab will be considered as related to the experimental arm.

All deaths after informed consent, irrespective of when they occur, are classified as Grade 5 AEs.

A TEAE is defined as any event with an onset date on or after the date of the first dose of study drug or any ongoing event on the date of the first dose of study drug that worsens in severity after the date of the first dose of study treatment. All TEAE will be judged as “related” or “not related” for each study treatment component by Investigator. Unless otherwise specified, only TEAEs with an onset date (or date of increase in severity) through the end of the Safety Observation Period (see Section 4.6) will be tabulated in summary tables.

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For the purpose of calculating treatment emergence and inclusion in summary tables, incomplete onset dates will be imputed as detailed in Appendix A. The calculations of percentages will be based on original unrounded values.

### 8.1.1. Immune-related Adverse Events

Immune-related adverse events (irAEs) are specific event or group of events that are considered immune-mediated. Each irAE category is a group of MedDRA Preferred Terms (PT). The list of MedDRA PT used to identify irAEs is revised and updated prior to analysis and the terms used for selection by categories will be provided. The incidence of treatment-emergent irAEs will be summarized by irAE category and PT.

An overall summary of AEs will be provided with the number and percent of subjects who experienced the following types of events during the safety observation period in each treatment arm:

- Subjects with a TEAE
- Subjects with a Related TEAE
- Subjects with a Serious TEAE
- Subjects with a Serious Related TEAE
- Subjects with a Worst Grade 3 or 4 TEAE
- Subjects with a Worst Grade 3 or 4 Related TEAE
- Subjects with a Worst Grade 4 TEAE
- Subjects with a Worst Grade 4 Related TEAE
- Subjects with a Grade 5 TEAE at any time (all deaths)
- Subjects with a Grade 5 TEAE (all deaths) at any time after first dose date and in the below categories:
  - ≤ 30 days of last dose of any study treatment (ie, on the Standard Safety Observation Period)
  - ≤ 30 days of last dose of any study treatment component (ie, on the Standard Safety Observation) and not causally related to disease under study
  - ≤ 100 days of last dose of any study treatment (ie, on the Extended Safety Observation Period)
  - ≤ 100 days of last dose of any study treatment component (ie, on the Extended Safety Observation Period) and not causally related to disease under study
- Subjects with a Related Grade 5 TEAE at any time after first dose date and those in the below categories:
  - ≤ 30 days of last dose of any study treatment (ie, on the Standard Safety Observation Period)

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  - ≤ 100 days of last dose of any study treatment (ie. on the Extended Safety Observation Period)
- Subjects with a TEAE leading to dose modification (reduction or hold/delay or incomplete infusion)
  - Subjects with a TEAE leading to dose reduction
  - Subjects with a TEAE leading to dose hold
  - Subjects with a TEAE leading to dose delay (of atezolizumab)
  - Subjects with a TEAE leading to infusion incomplete (of atezolizumab)
- Subjects with TEAE leading to treatment discontinuation
  - Discontinuation of any treatment component
    - Discontinuation of oral treatment component
    - Discontinuation of IV treatment component
  - Discontinuation of all treatment components
- Subjects with Related TEAE leading to treatment discontinuation
  - Discontinuation of any treatment component
    - Discontinuation of oral treatment component
    - Discontinuation of IV treatment component
  - Discontinuation of all treatment components
- Subjects with TEAE leading at any time to treatment discontinuation and TEAE is not related to treatment and not causally related to disease under study
  - Discontinuation of any treatment component
    - Discontinuation of oral treatment component
    - Discontinuation of IV treatment component
  - Discontinuation of all treatment components
- Subjects with TEAE at any time leading to treatment discontinuation and TEAE is not related to treatment and is causally related to disease under study
  - Discontinuation of any treatment component
    - Discontinuation of oral treatment component
    - Discontinuation of IV treatment component
  - Discontinuation of all treatment components

The following summaries of AEs will be provided in general for the standard Safety Observation Period for subjects in the Safety Population unless indicated otherwise (Table 15).

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**Table 15: Summaries of Adverse Events for Standard Observation Period**

| TEAE Included | Row-Levels (Sorted By) | Columns Will Display |
|---|---|---|
| ***Subject Incidence by SOC, Preferred Term and Severity*** | | |
| All | SOC and PT<br>(MedDRA standard) | Worst severity:<br>Any Grade, Grade 3/4, Grade 4, Grade 5 |
| ***Subject Incidence by Preferred Term and Severity*** | | |
| All | PT<br>(descending frequency of Any Grade) | Worst severity:<br>Any Grade, Grade 3/4, Grade 4, Grade 5 |
| All | PT<br>(descending frequency of Grade 3/4) | Worst severity:<br>Any Grade, Grade 3/4, Grade 4, Grade 5 |
| All | PT<br>(descending frequency of Any Grade) | Worst severity:<br>Any Grade, Grade 1, Grade 2, Grade 3, Grade 4, Grade 5 |
| Related | PT<br>(descending frequency of Any Grade)<br>PT<br>(descending frequency of Grade 3/4) | Worst severity:<br>Any Grade, Grade 3/4, Grade 4, Grade 5 |
| Serious (summarize for both standard and extended safety observation period) | PT<br>(descending frequency of Any Grade) | Worst severity:<br>Any Grades, Grade 3/4, Grade 4, Grade 5 |
| Related and serious (summarize for both standard and extended safety observation period) | PT<br>(descending frequency of Any Grade) | Worst severity:<br>Any Grades, Grade 3/4, Grade 4, Grade 5 |
| ***Leading to Treatment Modification and Discontinuations*** | | |
| Leading to dose reduction (applicable for oral components only) | PT<br>(descending frequency of Any Grade)<br>PT<br>(descending frequency of Grade 3/4) | Worst severity:<br>Any Grade, Grade 3/4, Grade 4, Grade 5 |
| Leading to dose hold/delay | PT<br>(descending frequency of Any Grade)<br>PT<br>(descending frequency of Grade 3/4) | Worst severity:<br>Any Grade, Grade 3/4, Grade 4, Grade 5 |

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| TEAE Included | Row-Levels (Sorted By) | Columns Will Display |
|---|---|---|
| Leading to dose modifications | PT (descending frequency of Any Grade)<br>PT (descending frequency of Grade 3/4) | Worst severity: Any Grade, Grade 3/4, Grade 4, Grade 5 |
| Leading to treatment discontinuation<br>• Of at least one component<br>• Of all components due to the same AE<br>• Of cabozantinib<br>• Of atezolizumab<br>• Of abiraterone or enzalutamide | PT (descending frequency of Any Grade) | Worst severity: Any Grades, Grade 3/4, Grade 4, Grade 5 |
| Leading to treatment discontinuation and related to treatment<br>• Of at least one component<br>• Of all components due to the same AE<br>• Of cabozantinib<br>• Of atezolizumab<br>• Of abiraterone or enzalutamide | PT (descending frequency of Any Grade) | Worst severity: Any Grades, Grade 3/4, Grade 4, Grade 5 |
| Leading to treatment discontinuation and not related to treatment<br>• Of at least one component<br>• Of all components due to the same AE<br>• Of cabozantinib<br>• Of atezolizumab<br>• Of abiraterone or enzalutamide | PT (descending frequency of Any Grade) | Worst severity: Any Grades, Grade 3/4, Grade 4, Grade 5 |
| Leading to treatment discontinuation and not related to study treatment and causally related to disease under study<br>• Of at least one component<br>• Of all components due to the same AE<br>• Of cabozantinib<br>• Of atezolizumab<br>• Of abiraterone or enzalutamide | PT (descending frequency of Any Grade) | Worst severity: Any Grades, Grade 3/4, Grade 4, Grade 5 |
| Leading to treatment discontinuation and not related to study treatment and not causally related to disease under study<br>• Of at least one component<br>• Of all components due to the same AE<br>• Of cabozantinib<br>• Of atezolizumab<br>• Of abiraterone or enzalutamide | PT (descending frequency of Any Grade) | Worst severity: Any Grades, Grade 3/4, Grade 4, Grade 5 |

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| TEAE Included | Row-Levels (Sorted By) | Columns Will Display |
|---|---|---|
| Immune-related | Category/PT (descending frequency of Any Grade) | Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5 |
| Grade 5 | PT (descending frequency of Grade 5) | Worst severity: Grade 5 |
| Grade 5 TEAEs judged not related to study treatment and not to be causally related to disease under study | PT (descending frequency of Grade 5) | Worst severity: Grade 5 |
| Gr 5 TEAEs Related to Study Treatment and ≤ 30 Days After the Last Dose of Study Treatment | PT (descending frequency of Grade 5) | Worst severity: Grade 5 |
| Gr 5 TEAEs Related to Study Treatment and ≤ 100 Days After the Last Dose of Study Treatment | PT (descending frequency of Grade 5) | Worst severity: Grade 5 |
| ***Subject Incidence by Special Criteria*** | | |
| Events with an incidence of ≥ 5% (Any Grade) in either arm or ≥ 2% (Grade 3/4) in the experimental arm | SOC and PT (SOC per MedDRA standard, PT within SOC by decreasing difference between arms for All Grades) | Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5 |
| Non-serious AEs of with an incidence of ≥ 5% in any arm (Any Grade) | SOC and PT (SOC per MedDRA standard, PT within SOC by decreasing difference between arms for All Grades) | Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5 |
| All | PT (descending frequency of difference in percent between the two arms for All Grades) | Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5 |
| All | PT (descending frequency of difference in percent between the two arms for Grade 3/4) | Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5 |

TEAE = treatment-emergent adverse events; SOC = system organ class; PT = preferred term

In some of the above summaries classified by treatment exposure and relationship, the counts and frequencies for the experimental arm (cabozantinib + atezolizumab) will be presented separately by individual treatment components as well as by combination.

The following data listings will also be provided with indicators for grade, relationship, seriousness, study day of the event start/stop, days since last dose, actions taken with study treatment:

- All AEs
- Grade 5 AEs (deaths)

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- Serious AEs other than death
- All AEs that led to treatment discontinuation
- All irAEs

### 8.1.2. Events to Monitor

Sponsor-defined ETMs, reflecting potential or identified risks, have been defined for cabozantinib. Each ETM consists of a grouped clinical concept comprising a broad set of AEs reflecting the concept. ETMs allow to assess those clinical concepts in a consistent, reproducible, and transparent way over time. These ETMs may also be described in the current cabozantinib product labeling (MTC US package insert and EU SmPC) or in the EU RMP document as known or potential risks.

The summaries to be provided for ETMs for the Safety Population for each treatment arm are presented in Table 16.

**Table 16: Summaries of Events to Monitor**

| TEAE Included | Row-Levels (Sorted By) | Columns Will Display |
|---|---|---|
| ***Subject Incidence by SOC, PT, and Severity*** | | |
| All ETM AEs | ETM and PT<br>(ETM, PT within ETM by descending frequency) | Worst severity:<br>Any Grade, Grade 3, Grade 4, Grade 5 |
| All ETM AEs of Grade ≥ 3 | ETM and PT<br>(ETM, PT within ETM by descending frequency) | Worst severity:<br>Grade ≥ 3, Grade 3, Grade 4, Grade 5 |
| ***Subject Incidence by Special Criteria*** | | |
| All ETM AEs by age (< 65 years, ≥ 65 years), ECOG, region, race) | ETM and PT<br>(ETM, PT within ETM by descending frequency) | Worst severity:<br>Any Grade, Grade 3, Grade 4, Grade 5 |
| ***Time to First Occurrence*** | | |
| All ETM AEs and Grade ≥ 3 | Time to first occurrence of Adverse Events to Monitor by Group Term | — |

TEAE = treatment-emergent adverse events; ETM = events to monitor; ECOG = Eastern Cooperative Oncology Group; PT = preferred term

## 8.2. Deaths

All subject deaths (Grade 5 TEAEs) will be summarized for all subjects in the Safety Population.

Deaths will be summarized as follows:

- Number of subjects who died
- Deaths ≤ 30 days after the date of receipt of the last dose of study treatment
- Deaths > 30 days to ≤ 100 days after the date of receipt of last dose of study treatment

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- Deaths > 100 days after the date of receipt of last dose of study treatment

In addition, under each category causality to study disease will also be summarized. All reported subject deaths will be listed.

## 8.3. Laboratory Assessments

### 8.3.1. Variables

Treatment-emergent laboratory abnormalities will be summarized as presented in Table 17. A treatment-emergent laboratory abnormality is defined as any laboratory abnormality with an onset date on or after the date of the first dose of study drug.

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**Table 17: Summaries of Treatment-Emergent Laboratory Abnormalities**

| Category | Abnormality | SDTM LBTESTCD | Grading System |
|---|---|---|---|
| **Hematology** | WBC increased<br>WBC decreased | WBC | CTCAE |
| | ANC increased<br>ANC decreased | NEUT | CTCAE |
| | Lymphocytes increased<br>Lymphocytes decreased | LYM | CTCAE |
| | Platelets increased<br>Platelets decreased | PLAT | CTCAE |
| | Hemoglobin increased<br>Hemoglobin decreased | HGB | CTCAE |
| **Serum chemistry** | Albumin decreased | ALB | CTCAE |
| | ALP increased | ALP | CTCAE |
| | Amylase increased | AMYLASE | CTCAE |
| | ALT increased | ALT | CTCAE |
| | AST increased | AST | CTCAE |
| | Corrected Calcium increased<br>Corrected Calcium decreased | CACR | CTCAE |
| | Creatinine increased | CREAT | CTCAE |
| | GGT increased | GGT | CTCAE |
| | Glucose increased<br>Glucose decreased | GLUC | CTCAE |
| | LDH increased | LDH | Sponsor |
| | Lipase increased | LIPASE | CTCAE |
| | Magnesium increased<br>Magnesium decreased | MG | CTCAE |
| | Phosphate increased<br>Phosphate decreased | PHOS | CTCAE |
| | Potassium increased<br>Potassium decreased | K | CTCAE |
| | Sodium increased<br>Sodium decreased | NA | CTCAE |
| | Total bilirubin increased | BILI | CTCAE |
| **Urine chemistry** | UPCR increased | PROTCRT | Sponsor |
| **Endocrinology**[a] | TSH increased<br>TSH decreased | TSH | HLN |
| | Free T4 increased<br>Free T4 decreased | T4FR | NA |

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a TSH is held in the SDTM "chemistry" laboratory category; will use HLN = high, low, normal classification based on normal range; NA=not applicable; Sponsor = Sponsor-defined grades.

Sponsor-defined grades are to be applied to the following analytes:

**LDH:**

- Grade 1 if > ULN to ≤ 2 × ULN
- Grade 2 if > 2 × ULN to ≤ 3 × ULN
- Grade 3 if > 3 × ULN

**UPCR:**

- Grade 1 if ≥ 17.0 to ≤ 121.0 mg/mmol (≥ 0.15 to ≤ 1.0 mg/mg)
- Grade 2 if > 121.0 to ≤ 396.0 mg/mmol (> 1.0 to < 3.5 mg/mg)
- Grade 3 if > 396.0 mg/mmol (> 3.5 mg/mg)

### 8.3.2. Analysis

All laboratory data parameters and visits will include flags for values above or below laboratory reference ranges. Toxicity grades will be assigned programmatically by applying the CTCAE v 5 guidelines. Only results with assessment dates through the end of the standard Safety Observation Period (see Section 4.6) will be tabulated in summary tables.

Laboratory summaries will be presented in SI units. Continuous laboratory test results will be summarized by treatment group using descriptive statistics for actual values and for changes from baseline by scheduled visit. Box plots at each scheduled visit (with visits shown on x-axis) may also be presented for some laboratory parameters. For test results which are below or above the quantification level, the imputed values as described in Appendix C will be used for deriving the grade and then summarized.

Tables summarizing baseline laboratory values and the incidence of laboratory abnormalities by baseline and maximum post-baseline CTCAE grade over all records will be presented. In addition, the following summaries will also be presented:

A. Liver function abnormalities will be assessed as follows:
   - Shift from baseline based on normal ranges
   - Summaries of subjects meeting Hy's Law laboratory screening criteria as shown below:
     – > 3 × ULN (ALT or AST), > 2 × ULN Total Bilirubin, and < 2 × ULN ALP
     – > 3 × ULN (ALT or AST), > 2 × ULN Total Bilirubin, and ≥ 2 × ULN ALP

B. Categorical summaries for baseline status for TSH and Free T4 will be presented. In addition, categorical summaries for post-baseline TSH and Free T4 status among subjects with TSH and Free T4 in the normal range at baseline will also be presented.

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For descriptive summaries of change from baseline in continuous laboratory variables and analyses of shift in grade from baseline or worst grade after baseline, all available results will be considered. The list of laboratory tests which will be included in the analysis are:

- Subject Incidence of treatment-emergent laboratory abnormalities in selected laboratory tests by CTCAE grade
- Change from baseline in laboratory values
- Shift from baseline in laboratory values by CTCAE grade
- Shift from baseline in laboratory values by High/Low/Normal
- Shift from baseline in laboratory values by Sponsor-defined grades
- Laboratory abnormalities with a subject incidence of ≥ 5% (all grades) or ≥ 2% (Grades 3-4) in experimental arm
- Laboratory abnormalities where subject incidence is at least ≥ 15% higher (all grades) in experimental arm compared with the control
- Laboratory abnormalities where subject incidence is at least ≥ 5% higher (Grades 3 and higher) in experimental arm compared with the control
- Worsening by at Least 2 Grades from Baseline in Selected Laboratory Tests

## 8.4. Vital Signs

### 8.4.1. Variables

The following vital signs will be summarized:

- Weight
- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)

### 8.4.2. Analysis

Subject incidence of clinically meaningful changes since baseline for weight and blood pressure will be presented as shown below:

- Proportion of subjects with weight loss ≥ 10% after first dose
- Subjects with at least 2 post-baseline assessments and who got worse since baseline and met the following blood pressure criteria on two or more visits (need not be consecutive) after first dose (JNC criteria were modified to include single measurement per time point when triplicate assessments were unavailable; Chobanian et al, 2003):
  - SBP 120-139 mmHg or DBP 80-89 mmHg
  - SBP 140-159 mmHg or DBP 90-99 mmHg
  - SBP ≥ 160 mmHg or DBP ≥ 100 mmHg

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Only results with assessment dates through the end of the standard safety observation period (see Section 4.6) will be considered for the summaries.

## 8.5. Electrocardiogram

Only results with assessment dates through the end of the standard safety observation period (see Section 4.6) will be considered for summaries. The following categorical summaries will be presented per Investigator if triplicate measurements were taken the average will be used:

- number of subjects with QTc > 500 ms after first dose
- number of subjects with increase in QTc from baseline of > 60ms after first dose per Investigator

For the above summaries, the most recent measurement taken before first dose will be used as baseline. If triplicate measurements were taken before first dose, the most recent average value from triplicate measurements taken before first dose will be used as baseline. If > 3 measurements are taken for an assessment, all will be included in the average.

## 8.6. Impact of COVID-19 Pandemic

Missed visits due to COVID-19 are captured on the CRFs and/or as protocol deviations. Summaries and analyses to describe and/or assess the impact of the COVID-19 pandemic will be included in the CSR. These may include tabulations of COVID-19 related protocol deviations and patterns of missing data, summaries of COVID-19 AEs, the addition of a Per Protocol Population, and comparative analyses of selected endpoint before, during, and after the pandemic.

## 8.7. Subgroup Analysis

The following subgroups based on baseline characteristics will be explored for all AEs and SAEs.

- Age category
  - < 65 years
  - 65 to < 75 years
  - ≥75 years
- Race
  - Asian
  - Black/African American
  - White
  - Other (race reported other than Asian, Black/African American, or White)
  - missing/not reported
- ECOG PS at baseline:

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  - 0
  - 1
  - ≥ 2
  - Missing
- Geographic Region
  - North America
  - Europe
  - Asia Pacific
  - Latin America

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# 9. IDENTIFICATION AND SUMMARY OF PROTOCOL DEVIATIONS

Important protocol deviations are prespecified in the study Protocol Deviation Management Plan. In accordance with ICH E3 (1995), important eligibility deviations per the inclusion/exclusion criteria (documented on study CRFs) and important post-randomization protocol deviations (tracked in study clinical trial management system, CTMS) will be identified and listed separately by study center and subject. Important deviations will be summarized for the ITT Population by deviation code (a standardized description [eg, “did not satisfy eligibility criteria” or “received prohibited medication”]) and deviation category (a standardized severity classification: “important” or “not important”). Important deviations will also be summarized for all 24 Ukraine subjects.

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# 10. DATA QUALITY ASSURANCE

The Clinical, Data Management, Biostatistics, and Medical Writing departments at Exelixis and designees will work diligently and collaboratively to ensure that the data collected and analyzed for this study are of the highest quality. In addition to electronic evaluation of the data and verification of data from source documents at the respective sites, a data review meeting will be held to review the data and correct significant data anomalies before the study database is locked or data are extracted for the purpose of analysis.

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# 11. CHANGES FROM PROTOCOL-SPECIFIED ANALYSES

Modifications to the planned statistical analyses should be minimized. However, the data obtained from the study may indicate that the planned analyses are inappropriate, the additional analyses need to be performed, or that the design of the study needs to be modified, due to factors such as the distribution of the data or imbalance in important covariates. The study report will provide a detailed explanation for deviations from the planned analyses.

The sentence “in the ORR analysis population at the later of OS IA1 data cutoff or when all enrolled subjects have had a chance to be followed for 6 months” is added after “If OS is significant at any analysis, re-allocate its 0.05 alpha to ORR and test ORR at 0.05” to clarify data cutoff to be used for ORR testing to ensure the control of familywise Type 1 error.

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# APPENDIX A. DATE IMPUTATION RULES

Incomplete Cancer Diagnosis Date

If *year* is missing (or completely missing): do not impute

If only *day* is missing: set to 15th of the month.

If *day* and *month* are missing: set to July 1st.

If either imputation rule above results in a diagnosis date > informed consent:

set diagnosis date to the date of informed consent - 1.

Incomplete Adverse Event Onset Date

Assumption: For on-study AEs.

If *year* is missing (or completely missing): set to the date of first dose.

If (*year* is present and *month* and *day* are missing) or (*year* and *day* are present and *month* is missing):

If *year* = year of first dose: set the date to the first dose date.

If *year* < year of first dose: set *month* and *day* to December 31st.

If *year* > year of first dose: set *month* and *day* to January 1st.

If *month* and *year* are present and *day* is missing:

If *year* = year of first dose, and:

If *month* = month of first dose: set *day* to day of first dose.

If *month* < month of first dose: set *day* to last day of *month*.

If *month* > month of first dose: set *day* to 1st day of *month*.

If *year* < year of first dose: set *day* to last day of month.

If *year* > year of first dose: set *day* to 1st day of month.

For all other cases: set to date of first dose.

Do not impute start/stop dates for incomplete prior radiation, prior surgery/procedures, and prior transfusions.

Incomplete for Start Date for prior and concomitant medication and prior anticancer therapy.

If *year* is missing (or completely missing):

Set to last dose date + 1

If (*year* is present and *month* and *day* are missing) or (*year* and *day* are present and *month* is missing):

If *year* > year of last dose: set *month* and *day* to January 1st.

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If *year* = year of last dose: set the date to the last dose of study treatment + 1.

If *year* < year of last dose: set *month* and *day* to December 31st.

If *year* and *mont*h are present and *day* is missing:

Set *day* to 1st day of month.

Incomplete Prior and Concomitant Medication End Date (Do not impute for prior anticancer therapies)

If *year* is missing (or completely missing): do not impute.

If (*year* is present and *month* and *day* are missing) or (*year* and *day* are present and *month* is missing):

Set *month* and *day* to December 31st.

If *year* and *month* are present and *day* is missing:

Set *day* to last day of the month.

Incomplete Concomitant and Subsequent Anticancer Therapy Start Date

Assumption: Anticancer therapies reported on the Concomitant and Subsequent Anticancer Therapy CRF.

If *year* is missing (or completely missing): set to date of last dose of study treatment + 1

If (*year* is present and *month* and *day* are missing) or (*year* and *day* are present and *month* is missing):

If *year* > year of the last dose: Set *month* and *day* to January 1st.

If *year* = year of the last dose: Set *month* and *day* to date of last dose of study treatment + 1

If *year* and *month* are present and *day* is missing:

Set *day* to 1st day of month if the resulting imputed date is greater than date of last dose or if the month is before the month of last dose date and year is same or before the year of the last dose date. Otherwise set the imputed date to date of last dose + 1

Incomplete Death Date

Identify date of last known alive (LA) prior to death from the following:

1. Date of decision to discontinue study treatment from End of Treatment CRF
2. Date of last radiographic assessment from End of Radiographic Follow-Up CRF
3. Date LAs from Survival Follow-Up CRF
4. Date of last lab assessment from the Labs dataset

If *year* is missing (or completely missing): set to date of LA + 1

If only *day* is missing: set to the maximum of the first of month or LA + 1

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If *month* and *day* are missing:

If *year* of LA = year of death

Set death date to date of LA + 1

If *year* of LA< year of death

Set *month* and day to Jan 1st.

Incomplete Oral Study Treatment Start Date

Define previous sequential dosing "milestone" as the latest of previous dose stop date, previous dose hold stop date, date of first dose or randomization date.

If *year* is missing (or completely missing): set to date of previous sequential dosing "milestone" + 1

If (*year* is present and *month* and *day* are missing) or (*year* and *day* are present and *month* is missing): set to January 1st

If *year* and *month* are present and *day* is missing: set to the first day of the month

If the imputed date is before the previous sequential dosing "milestone": set to the date of previous sequential dosing "milestone" + 1

Incomplete Oral Study Treatment Stop Date

Define next sequential dosing "milestone" as the earliest of next dose start date, next dose hold start date, date of last dose from EOT CRF or the cutoff date.

If *year* is missing (or completely missing): set to date of next sequential dosing "milestone" - 1

If (*year* is present and *month* and *day* are missing) or (*year* and *day* are present and *month* is missing): set to December 31st

If *year* and *month* are present and *day* is missing: set to the last day of the month

If the imputed date is after the next sequential dosing "milestone": set to the date of next sequential dosing "milestone" - 1

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# APPENDIX B. ROUNDING RULES FOR REPORTED PERCENTAGES

For percentages ≥ 10%:

- Values ≥ X.5 or above round to X + 1.
- Values > X but < X.5 round to X.

For percentages <10%:

- Values ≥ X.Y5 or above round to X.Y + 0.1.
- Values > X.Y but < X.Y5 round to X.Y.

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# APPENDIX C. IMPUTATION RULES FOR LABORATORY VALUES OUTSIDE OF QUANTIFICATION RANGE

- Lab values below the lower level of quantification (LLQ) that are reported as "< LLQ" or "≤ LLQ" in the database will be imputed by LLQ × 0.99 for analysis purposes; however, the original value will also be maintained.
- Lab values above the upper level of quantification (ULQ) that are reported as "> ULQ" or "≥ ULQ" in the database will be imputed by ULQ × 1.01 for analysis purposes; however, the original value will also be maintained.

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# APPENDIX D. EQ-5D-5L INDEX VALUE CONVERSION GUIDELINES

The UK EQ-index will be obtained by mapping EQ-5D-5L health states to EQ-5D-3L value sets using the cross-walk method (Van Hout, 2012).

- Calculate ***health state***
  - Each of the five dimensions comprising the EQ-5D descriptive system is divided into five levels of perceived problems:
    - Level 1: indicating no problem
    - Level 2: indicating slight problems
    - Level 3: indicating moderate problems
    - Level 4: indicating severe problems
    - Level 5: indicating extreme problems

- A unique health state is defined by combining one level from each of the five dimensions (based on the order: Mobility, Self-care, Usual Activities, Pain/Discomfort, and Anxiety/Depression).

  For example, state 11111 indicates no problems on any of the five dimensions, while state 12345 indicates no problems with mobility, slight problems with washing or dressing, moderate problems with doing usual activities, severe pain or discomfort and extreme anxiety or depression. Note that missing values will be coded as '9'. Ambiguous values will be treated as missing values.

- ***EQ-index values*** for the UK are obtained based on the cross-walk method (EQ-5D-5L User Guide; Dolan, 2022).

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# APPENDIX E. EORTC QLQ-C30 QUESTIONNAIRE, ENGLISH SAMPLE VERSION 3

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ☐☐☐☐

Your birthdate (Day, Month, Year): ☐☐☐☐☐☐☐☐

Today's date (Day, Month, Year): ☐☐☐☐☐☐☐☐

| | | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|---|
| 1. | Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase? | 1 | 2 | 3 | 4 |
| 2. | Do you have any trouble taking a long walk? | 1 | 2 | 3 | 4 |
| 3. | Do you have any trouble taking a short walk outside of the house? | 1 | 2 | 3 | 4 |
| 4. | Do you need to stay in bed or a chair during the day? | 1 | 2 | 3 | 4 |
| 5. | Do you need help with eating, dressing, washing yourself or using the toilet? | 1 | 2 | 3 | 4 |
| **During the past week:** | | **Not at All** | **A Little** | **Quite a Bit** | **Very Much** |
| 6. | Were you limited in doing either your work or other daily activities? | 1 | 2 | 3 | 4 |
| 7. | Were you limited in pursuing your hobbies or other leisure time activities? | 1 | 2 | 3 | 4 |
| 8. | Were you short of breath? | 1 | 2 | 3 | 4 |
| 9. | Have you had pain? | 1 | 2 | 3 | 4 |
| 10. | Did you need to rest? | 1 | 2 | 3 | 4 |
| 11. | Have you had trouble sleeping? | 1 | 2 | 3 | 4 |
| 12. | Have you felt weak? | 1 | 2 | 3 | 4 |
| 13. | Have you lacked appetite? | 1 | 2 | 3 | 4 |
| 14. | Have you felt nauseated? | 1 | 2 | 3 | 4 |
| 15. | Have you vomited? | 1 | 2 | 3 | 4 |
| 16. | Have you been constipated? | 1 | 2 | 3 | 4 |

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| During the past week: | | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|---|
| 17. | Have you had diarrhea? | 1 | 2 | 3 | 4 |
| 18. | Were you tired? | 1 | 2 | 3 | 4 |
| 19. | Did pain interfere with your daily activities? | 1 | 2 | 3 | 4 |
| 20. | Have you had difficulty in concentrating on things, like reading a newspaper or watching television? | 1 | 2 | 3 | 4 |
| 21. | Did you feel tense? | 1 | 2 | 3 | 4 |
| 22. | Did you worry? | 1 | 2 | 3 | 4 |
| 23. | Did you feel irritable? | 1 | 2 | 3 | 4 |
| 24. | Did you feel depressed? | 1 | 2 | 3 | 4 |
| 25. | Have you had difficulty remembering things? | 1 | 2 | 3 | 4 |
| 26. | Has your physical condition or medical treatment interfered with your family life? | 1 | 2 | 3 | 4 |
| 27. | Has your physical condition or medical treatment interfered with your social activities? | 1 | 2 | 3 | 4 |
| 28. | Has your physical condition or medical treatment caused you financial difficulties? | 1 | 2 | 3 | 4 |

## For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1 2 3 4 5 6 7

Very poor Excellent

30. How would you rate your overall quality of life during the past week?

1 2 3 4 5 6 7

Very poor Excellent

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# APPENDIX F. ESTIMANDS TERMINOLOGY

Source: ICH E9 R1

**Estimand Attributes:**

| # | Estimand Attribute |
|---|---|
| 1 | The treatment, that is, experimental versus control treatment. |
| 2 | The population, that is, the patients targeted by the scientific question. |
| 3 | The variable (or endpoint), to be obtained for each patient, that is required to address the scientific question. |
| 4 | The specification of how to account for intercurrent events to reflect the scientific question of interest. |
| 5 | The population-level summary for the variable which provides, as required, a basis for a comparison between treatment conditions. |

**Strategies for Addressing Intercurrent Event(s):**

| Strategy | Description |
|---|---|
| Treatment policy | The occurrence of the intercurrent event is irrelevant: the value for the variable of interest is used regardless of whether or not the intercurrent event occurs. |
| Composite | The occurrence of the intercurrent event is taken to be a component of the variable, ie, the intercurrent event is integrated with one or more other measures of clinical outcome as the variable of interest. |
| Hypothetical | A scenario is envisaged in which the intercurrent event would not occur: the value to reflect that scientific question of interest is that which the variable would have taken in the hypothetical scenario defined. |
| Principal stratum | The target population might be taken to be the principal stratum in which an intercurrent event would not occur. |
| While on treatment | Response to treatment prior to the occurrence of the intercurrent event is of interest. |

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