

**Official Title:** A Phase III, Multicenter, Randomized Study of Atezolizumab (Anti-PD-L1 Antibody) in Combination With Enzalutamide Versus Enzalutamide Alone in Patients With Metastatic Castration-Resistant Prostate Cancer After Failure of an Androgen Synthesis Inhibitor and Failure of, Ineligibility for, or Refusal of a Taxane Regimen

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## PROTOCOL

**TITLE:** A PHASE III, MULTICENTER, RANDOMIZED STUDY OF ATEZOLIZUMAB (ANTI-PD-L1 ANTIBODY) IN COMBINATION WITH ENZALUTAMIDE VERSUS ENZALUTAMIDE ALONE IN PATIENTS WITH METASTATIC CASTRATION-RESISTANT PROSTATE CANCER AFTER FAILURE OF AN ANDROGEN SYNTHESIS INHIBITOR AND FAILURE OF, INELIGIBILITY FOR, OR REFUSAL OF A TAXANE REGIMEN

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**MEDICAL MONITOR:** [REDACTED], M.D., Ph.D.  
**SPONSOR:** F. Hoffmann-La Roche Ltd  
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### PROTOCOL AMENDMENT APPROVAL

**Date and Time (UTC)**  
14-Feb-2020 17:27:37

**Title**  
Company Signatory

**Approver's Name**  
[REDACTED]

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## PROTOCOL AMENDMENT, VERSION 8: RATIONALE

Protocol CO39385 has been amended to align with the Atezolizumab Investigator's Brochure. Changes to the protocol, along with a rationale for each change, are summarized below:

- To align with the Atezolizumab Investigator's Brochure, Version 15, "immune-related" has been changed to "immune-mediated" when describing events associated with atezolizumab (Section 3.2 and throughout Section 5).
- To address a request [REDACTED] [REDACTED] systemic immune activation has been replaced by hemophagocytic lymphohistiocytosis and macrophage activation syndrome in the list of potential risks for atezolizumab (Section 5.1.1) and the management guidelines for systemic immune activation have been replaced with management guidelines for hemophagocytic lymphohistiocytosis and macrophage activation syndrome (Section 5.1.4.3 and Table 3). In addition, systemic immune activation has been removed from the list of adverse events of special interest (Section 5.2.3).
- The management guidelines for infusion-related reactions associated with atezolizumab have been updated to include guidelines for cytokine-release syndrome (CRS) to align with the definition, grading, and management of CRS reflected in a recent publication (Lee et al. 2019) (Section 5.1.4.3 and Table 3).
- The requirement for completing the patient diary has been removed from the Schedule of Activities to align with the Informed Consent Form (Appendix 1).

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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**PROTOCOL AMENDMENT ACCEPTANCE FORM**

**TITLE:** A PHASE III, MULTICENTER, RANDOMIZED STUDY OF ATEZOLIZUMAB (ANTI-PD-L1 ANTIBODY) IN COMBINATION WITH ENZALUTAMIDE VERSUS ENZALUTAMIDE ALONE IN PATIENTS WITH METASTATIC CASTRATION-RESISTANT PROSTATE CANCER AFTER FAILURE OF AN ANDROGEN SYNTHESIS INHIBITOR AND FAILURE OF, INELIGIBILITY FOR, OR REFUSAL OF A TAXANE REGIMEN

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**MEDICAL MONITOR:** [REDACTED], M.D., Ph.D.

**SPONSOR:** F. Hoffmann-La Roche Ltd

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

\_\_\_\_\_  
Principal Investigator's Name (print)

\_\_\_\_\_  
Principal Investigator's Signature

\_\_\_\_\_  
Date

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

## PROTOCOL SYNOPSIS

**TITLE:** A PHASE III, MULTICENTER, RANDOMIZED STUDY OF ATEZOLIZUMAB (ANTI-PD-L1 ANTIBODY) IN COMBINATION WITH ENZALUTAMIDE VERSUS ENZALUTAMIDE ALONE IN PATIENTS WITH METASTATIC CASTRATION-RESISTANT PROSTATE CANCER AFTER FAILURE OF AN ANDROGEN SYNTHESIS INHIBITOR AND FAILURE OF, INELIGIBILITY FOR, OR REFUSAL OF A TAXANE REGIMEN

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**VERSION NUMBER:** 8

**EUDRACT NUMBER:** 2016-003092-22

**IND NUMBER:** 131196

**TEST PRODUCTS:** Atezolizumab (RO5541267) and enzalutamide

**PHASE:** III

**INDICATION:** Metastatic castration-resistant prostate cancer

**SPONSOR:** F. Hoffmann-La Roche Ltd

### **Objectives and Endpoints**

This is a Phase III, multicenter, randomized open-label study designed to evaluate the efficacy and safety of atezolizumab in combination with enzalutamide compared with enzalutamide alone in patients with metastatic castration-resistant prostate cancer (mCRPC) after failure of an androgen synthesis inhibitor and failure of, ineligibility for, or refusal of a taxane regimen. Specific objectives and corresponding endpoints for the study are outlined below.

### Objectives and Corresponding Endpoints

Primary Efficacy Objective	Corresponding Endpoint
<ul style="list-style-type: none"> <li>To evaluate the efficacy of atezolizumab/enzalutamide compared with enzalutamide alone</li> </ul>	<ul style="list-style-type: none"> <li>OS, defined as the time from randomization to death from any cause</li> </ul>
Country-Specific Objective for China	Corresponding Endpoint
<ul style="list-style-type: none"> <li>To evaluate the efficacy of atezolizumab/enzalutamide compared with enzalutamide alone in patients who are residents of China</li> </ul>	<ul style="list-style-type: none"> <li>Same as the primary objective</li> </ul>
Secondary Efficacy Objective	Corresponding Endpoints
<ul style="list-style-type: none"> <li>To evaluate the efficacy of atezolizumab/enzalutamide compared with enzalutamide alone</li> </ul>	<ul style="list-style-type: none"> <li>OS probability at 12 and 24 months</li> <li>Time to first SSE               <p>An SSE is defined as external beam radiation therapy to relieve skeletal symptoms (including initiation of radium-223 dichloride or other types of radionuclide therapy to treat symptoms of bone metastases), new symptomatic pathologic bone fracture, clinically apparent occurrence of spinal cord compression, or tumor related orthopedic surgical intervention.</p> </li> <li>rPFS, as assessed by the investigator, and adapted from the PCWG3 criteria. rPFS is defined as the time from randomization to the earliest occurrence of one of the following:               <p>A patient is considered to have progressed by bone scan if:</p> <p>The first bone scan with <math>\geq 2</math> new lesions compared to baseline is observed <math>&lt; 12</math> weeks from randomization and is confirmed by a second bone scan taken <math>\geq 6</math> weeks later showing <math>\geq 2</math> additional new lesions (a total of <math>\geq 4</math> new lesions compared to baseline); the date of progression is the date of the first post-treatment scan, OR</p> <p>After the first post-treatment scan, <math>\geq 2</math> new lesions are observed relative to the first post-treatment scan, which is confirmed on a subsequent scan <math>\geq 6</math> weeks later; the date of progression is the date of the post-treatment scan when <math>\geq 2</math> new lesions were first documented.</p> <p>Progression of soft tissue lesions, as defined per PCWG3 modified RECIST v1.1</p> <p>Death from any cause</p> </li> <li>rPFS probability at 6 and 12 months</li> </ul>

**Objectives and Corresponding Endpoints (cont.)**

<b>Secondary Efficacy Objective (cont.)</b>	<b>Corresponding Endpoints</b>
<p>To evaluate the efficacy of atezolizumab/enzalutamide compared with enzalutamide alone (cont.)</p>	<ul style="list-style-type: none"> <li>• PSA response rate, defined as a &gt; 50% decrease in PSA from baseline that is confirmed after <math>\geq 3</math> weeks by a consecutive confirmatory PSA measurement</li> <li>• Time to PSA progression, defined as the time from randomization to the time of PSA progression, as defined per the PCWG3 criteria: <ul style="list-style-type: none"> <li>In patients with no PSA decline from baseline, PSA progression is defined as a <math>\geq 25\%</math> increase and an absolute increase of <math>\geq 2</math> ng/mL above the baseline value, <math>\geq 12</math> weeks after baseline.</li> <li>In patients with an initial PSA decline from baseline, PSA progression is defined as a <math>\geq 25\%</math> increase and an absolute increase of <math>\geq 2</math> ng/mL above the nadir value, which is confirmed by a consecutive second value obtained <math>\geq 3</math> weeks later.</li> </ul> </li> <li>• Objective response rate in soft tissue lesions, defined as the proportion of patients with either a CR or PR on two consecutive occasions <math>\geq 6</math> weeks apart, as determined by the investigator through use of PCWG3 criteria</li> </ul>
<b>Exploratory Efficacy Objective</b>	<b>Corresponding Endpoints</b>
<ul style="list-style-type: none"> <li>• To evaluate the efficacy of atezolizumab/enzalutamide compared with enzalutamide alone</li> </ul>	<ul style="list-style-type: none"> <li>• DOR in soft tissue lesions, defined for patients who had an objective response in soft tissue as the time from the first documented objective response in soft tissue to radiographic disease progression, as determined by the investigator through use of PCWG3 criteria</li> <li>• DCR, defined as the proportion of patients with a best response of confirmed CR or PR or stable disease in soft tissue lesions per PCWG3-modified RECIST v1.1 and/or no confirmed radiographic disease progression on bone scan per PCWG3 criteria</li> <li>• Modified progression free survival based on radiographic disease progression and unequivocal clinical progression, defined as the time from randomization to the earliest occurrence of one of the following: <ul style="list-style-type: none"> <li>Radiographic disease progression per PCWG3 criteria (as defined above)</li> <li>Unequivocal clinical progression characterized as at least one of the following: <ul style="list-style-type: none"> <li>Symptomatic skeletal-related event (as defined above)</li> <li>Deterioration in ECOG performance status by at least two points that is attributed to disease progression</li> <li>Initiation of next systemic anti-cancer therapy</li> </ul> </li> </ul> </li> </ul>

**Objectives and Corresponding Endpoints (cont.)**

<b>Safety Objective</b>	<b>Corresponding Endpoints</b>
<ul style="list-style-type: none"> <li>To evaluate the safety and tolerability of atezolizumab and enzalutamide compared with enzalutamide alone</li> </ul>	<ul style="list-style-type: none"> <li>Incidence, nature, frequency, and severity of adverse events, with severity determined through use of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v4.0)</li> <li>Clinically significant changes in vital signs, and clinical laboratory results during and following study treatment administration</li> </ul>
<b>Pharmacokinetic Objectives</b>	<b>Corresponding Endpoints</b>
<ul style="list-style-type: none"> <li>To characterize the pharmacokinetics of atezolizumab when given in combination with enzalutamide</li> <li>To characterize the pharmacokinetics of enzalutamide and its active metabolite N-desmethyl enzalutamide when enzalutamide is administered alone or in combination with atezolizumab</li> </ul>	<ul style="list-style-type: none"> <li>Serum concentration of atezolizumab at specified timepoints</li> <li>Plasma concentration of enzalutamide and N-desmethyl enzalutamide at specified timepoints in the safety run-in phase and in a PK cohort in the randomized phase (approximately 30 patients per treatment arm)</li> </ul>
<b>Exploratory Biomarker Objective</b>	<b>Corresponding Endpoints</b>
<ul style="list-style-type: none"> <li>To identify biomarkers that are predictive of response to atezolizumab and/or enzalutamide (i.e., predictive biomarkers), are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to atezolizumab and/or enzalutamide, are associated with susceptibility to developing adverse events, can provide evidence of atezolizumab and/or enzalutamide activity, or can increase the knowledge and understanding of disease biology on the basis of the following endpoint:</li> </ul>	<ul style="list-style-type: none"> <li>Relationship between biomarkers in blood, urine, and tumor tissue and efficacy, safety, PK, immunogenicity, or other biomarker endpoints</li> </ul>

## Objectives and Corresponding Endpoints (cont.)

<b>Immunogenicity Objective</b>	<b>Corresponding Endpoint</b>
• To evaluate the immune response to atezolizumab	• Incidence of anti-therapeutic antibodies (ATAs) against atezolizumab
<b>Exploratory Immunogenicity Objective</b>	<b>Corresponding Endpoint</b>
• To evaluate potential effects of ATAs	• Relationship between ATA status and efficacy, safety, or PK endpoints

AQA=analgesic quantification algorithm; ATA=anti-therapeutic antibody; CR=complete response; CRPC=castration-resistant prostate cancer; DCR=disease control rate; DOR=duration of response; ECOG=Eastern Cooperative Oncology Group; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; OS=overall survival; PCWG3=Prostate Cancer Working Group 3; PF=physical function; PFS=progression-free survival; PK=pharmacokinetic; PR=partial response; PSA=prostate-specific antigen; rPFS=radiographic progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumors; SSE=symptomatic skeletal event.

## **Study Design**

### **Description of Study**

This is a Phase III, multicenter, randomized, open-label study designed to evaluate the safety and efficacy of atezolizumab in combination with enzalutamide compared with enzalutamide alone in patients with mCRPC after failure of an androgen synthesis inhibitor (e.g., abiraterone) and failure of, ineligibility for, or refusal of a taxane regimen.

The study will include the following patients:

- Patients who have progressed during treatment with an androgen synthesis inhibitor (e.g., abiraterone) for prostate cancer and have received a prior taxane regimen for metastatic hormone-sensitive and/or metastatic castration-resistant prostate cancer
- Patients who have progressed during treatment with an androgen synthesis inhibitor (e.g., abiraterone) for prostate cancer and who are not fit enough to receive a taxane regimen for mCRPC
- Patients who have progressed during treatment with an androgen synthesis inhibitor (e.g., abiraterone) for prostate cancer and who decline a taxane regimen for mCRPC after an informed discussion

Approximately 180 sites globally will participate in the study and approximately 730 patients will be enrolled (first 10 patients in the safety run-in cohort followed by 720 patients in the global randomized phase).

The Sponsor recommends that investigators use their clinical judgment to determine if the patients who remain on the study appear to be benefitting from their therapy, and discuss the benefits and risks with patients of remaining on their current treatment. Patients who remain on treatment until the closure of the study will be able to continue to receive treatment as part of a post-trial access program. Patients may start transferring to the program after the required approvals are available (as applicable).

### **Safety Run-In Phase**

In the safety run-in phase of the study, 10 patients will be enrolled and will receive atezolizumab in combination with enzalutamide. After 10 patients have been enrolled, enrollment will be stopped temporarily and all patients will be monitored closely for adverse events until the last patient has completed the first cycle (21 days). Patients will continue to receive study treatment and be followed for safety and efficacy per the schedule of activities.



After 10 patients have received study treatment and completed at least one cycle of study treatment (21 days), an independent Data Monitoring Committee (iDMC) will review available data and make a recommendation regarding initiation of the randomized phase of the study.

### **Randomized Phase**

Enrollment in the randomized phase of the study will be initiated after review of the safety run-in data by the iDMC and the Sponsor. Approximately 720 patients will be enrolled in the randomized phase of the study. Patients will be randomized to one of the following treatment arms in a 1:1 ratio (experimental to control arm):

- Arm A (experimental arm): atezolizumab in combination with enzalutamide
- Arm B (control arm): enzalutamide alone

Randomization will be conducted with the aid of an interactive voice/Web response system (IxRS).

The randomization will be stratified by the following stratification factors:

- Prior taxane-containing regimen for mCRPC, defined as at least 2 cycles of a taxanes-containing regimen (yes vs. no)
- Presence of liver metastasis (yes vs. no)
- LDH  $\leq$  upper limit of normal (ULN) vs.  $>$  ULN
- Pain severity (Brief Pain Inventory Short Form [BPI-SF]) Question 3 assessing pain at its worst over the past 24 hours [score  $<$  4 vs.  $\geq$  4]

A stratified permuted-block randomization will be implemented to balance treatment assignment within stratum levels.

Patient recruitment will be capped with respect to two of the stratification factors: the proportion of patients who have not received a prior taxane-containing regimen for mCRPC will be approximately 50% or less, and the proportion of patients with liver metastases at baseline will be approximately 10% or less. Presence of liver metastases will be determined based on computed tomography (CT) or magnetic resonance imaging (MRI) scan. The purpose of the cap is to ensure the prevalence of these two prognostic factors in the study population will be similar to that reported in the targeted population.

Atezolizumab will be administered at a fixed dose of 1200 mg by intravenous (IV) infusion on Day 1 of each 21-day cycle until investigator-assessed confirmed radiographic disease progression per Prostate Cancer Working Group 3 (PCWG3) or unacceptable toxicity.

Enzalutamide will be administered orally at a dose of 160 mg (four 40-mg capsules) daily until investigator-assessed confirmed radiographic disease progression per PCWG3 or unacceptable toxicity.

Patients will be permitted to continue study treatment after PCWG3 criteria are met for confirmed radiographic disease progression if they meet all of the following criteria (treatment until they are no longer clinically benefiting per PCWG3 recommendation).

- Evidence of clinical benefit as assessed by the investigator
- Absence of symptoms and signs indicating unequivocal progression of disease
- No decline in Eastern Cooperative Oncology Group (ECOG) Performance Status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed and stabilized by protocol-allowed medical interventions
- Written consent to acknowledge deferring other treatment options in favor of continuing study treatment at the time of initial disease progression

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

Patients with rising prostate-specific antigen (PSA) levels only (i.e., in the absence of confirmed radiographic or clinical progression) should remain on study treatment per PCWG3 criteria and recommendations. PSA rise without evidence of confirmed radiographic progression or a symptomatic skeletal-related event is strongly discouraged as a criterion to start a new systemic

anti-neoplastic therapy during the first 12 weeks of therapy and is discouraged as a criterion to start a new systemic anti-neoplastic therapy throughout the study.

Focal palliative radiography (e.g., external-beam radiotherapy to address single sites of disease), initiation of bisphosphonates or denosumab, standard-of-care corticosteroid use of no greater than the equivalent of 10 mg of prednisone or prednisolone per day and pain management are allowed and should not result in discontinuation of study treatment. However, patients should be evaluated for clinically apparent symptomatic skeletal events (SSEs).

Initiation of radium-223 dichloride to manage symptomatic bone lesions is not permitted during study treatment.

Patients will undergo scheduled tumor assessments at baseline and every 9 weeks ( $\pm 3$  days) for the first 27 weeks and every 12 weeks ( $\pm 6$  days) thereafter until confirmed radiographic disease progression per PCWG3. In the absence of confirmed radiographic progression, tumor assessments should continue, regardless of whether patients start new anti-cancer therapy, until death, loss of follow-up, withdrawal of consent, or study termination by the Sponsor, whichever occurs first. For patients who continue to receive study treatment following confirmed disease progression, assessments will continue until loss of clinical benefit.

All primary imaging data used for tumor assessments may be collected by the Sponsor to enable the possibility of a centralized, independent review of response endpoints by an Independent Review Facility (IRF).

Safety assessments will include the incidence, nature, and severity of adverse events and laboratory abnormalities graded per the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0. Laboratory safety assessments will include the regular monitoring of hematology and blood chemistry.

Serum samples will be collected in patients in Arm A (atezolizumab and enzalutamide) to monitor atezolizumab pharmacokinetics and to detect the presence of antibodies to atezolizumab. Plasma samples to monitor enzalutamide and N-desmethyl enzalutamide pharmacokinetics will also be collected in the safety run-in phase and in a pharmacokinetic (PK) cohort in the randomized phase (approximately 30 patients per treatment arm). Patient samples, including archival tumor tissues, as well as urine, serum, plasma and whole blood, will be collected for future exploratory biomarker assessments for all patients in the randomized phase.

It is recommended that patients undergo tumor biopsy sample collection, if deemed clinically feasible by the investigator, at the time of first evidence of confirmed radiographic disease progression according to PCWG3 criteria (within 40 days after confirmed radiographic progression or prior to the start of new anti-cancer treatment, whichever is sooner). These samples will be analyzed to evaluate the utility of the biopsy in distinguishing pseudoprogression (caused by tumor-infiltrating immune cells [ICs]) from true progression. In addition, tumor tissue biomarkers related to resistance, disease progression, and clinical benefit of atezolizumab may be analyzed.

Patients who are withdrawn from study treatment will be evaluated within 30 days and approximately 120 days after last study treatment for a treatment discontinuation visit and safety visit, respectively. Thereafter, patients will enter a post-trial access program (as applicable).

### **Number of Patients**

Approximately 180 sites globally will participate in the study and approximately 730 patients will be enrolled.

### **Target Population**

#### Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age  $\geq 18$  years
- Ability to comply with the study protocol, in the investigator's judgment
- ECOG performance status of 0 or 1
- Life expectancy  $\geq 3$  months

- Histologically confirmed adenocarcinoma of the prostate
  - Disease must be either metastatic or locally confined inoperable disease that cannot be treated with definitive intent (no chance for a curative intervention)
  - Patients presenting with treatment emergent neuroendocrine differentiation, but not primary small cell features, are eligible
- Known castrate-resistant disease, defined as meeting all of the following criteria:
  - Castrate serum testosterone level  $\leq 50$  ng/dL (1.7 nmol/L) at the screening visit
  - Bilateral orchiectomy or maintenance on androgen ablation therapy with luteinizing hormone-releasing hormone agonist or antagonist or polyestradiol phosphate for the duration of the study (including the follow-up period)
- Progressive disease prior to screening by PSA or imaging per PCWG3 criteria during or following the direct prior line of therapy in the setting of medical or surgical castration. Disease progression for study entry is defined as one or more of the following three criteria:
  - PSA progression defined as two increases in PSA over a previous reference value of  $\geq 1$  ng/mL ( $\mu\text{g/L}$ ) as the minimum starting value (i.e., a minimum of 3 PSA values total), with each progression measurement at least 1 week apart
  - Soft tissue disease progression defined by RECIST v1.1
    - Previously normal ( $< 1.0$  cm) lymph nodes must have grown by  $\geq 5$  mm in the short axis to be considered to have progressed
  - Bone disease progression defined by two or more new lesions on bone scan
- One prior regimen/line of a taxane-containing regimen for mCRPC or refusal or ineligibility of a taxane-containing regimen
  - Patients who have received a taxane-containing regimen for metastatic HSPC are eligible.
  - Patients who refuse or are ineligible for a taxane-containing regimen are eligible for enrollment if they have no intention to use cytotoxic chemotherapy within the next 6 months after an informed discussion.
  - A taxane-containing treatment should be considered in patients with symptomatic and extensive visceral disease who have not previously received and are good candidates for a taxane-containing regimen.
- Progression on a prior regimen/line of an androgen synthesis inhibitor for prostate cancer (e.g., abiraterone, orteronel or galeterone)
  - Patients must have received at least 28 days of an androgen synthesis inhibitor.
  - Prior treatment with first generation antiandrogens (e.g., nilutamide, bicalutamide), oral ketoconazole, vaccines (e.g., sipuleucel-T, prostvac VF), and radium-223 dichloride is also allowed in addition to one prior regimen or line of an androgen synthesis inhibitor for prostate cancer.
- Patients receiving bisphosphonate or denosumab therapy must have been on a stable dose for at least 4 weeks.
- Availability of a representative tumor specimen from a site not previously irradiated that is suitable for determination of PD-L1 status via central testing
  - A formalin-fixed, paraffin-embedded (FFPE) tumor specimen in a paraffin block (preferred) or at least 15 slides containing unstained, freshly cut, serial sections must be submitted along with an associated pathology report prior to study enrollment. If only 10–14 slides are available, the patient may still be eligible for the study, after discussion with and approval by the Medical Monitor. If archival tumor tissue is unavailable or is determined to be unsuitable for required testing, tumor tissue must be obtained from a biopsy performed at screening. No tissue will be collected for patients enrolled in the safety run-in phase. Tissue from bone metastases might be acceptable after consultation with the Medical Monitor.

- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment:
  - ANC  $\geq 1.5 \times 10^9/L$  (without granulocyte colony-stimulating factor support within 2 weeks prior to Cycle 1, Day 1)
  - Lymphocyte count  $\geq 0.5 \times 10^9/L$
  - Platelet count  $\geq 100 \times 10^9/L$  without transfusion
  - Hemoglobin  $\geq 9$  g/dL

Patients may be transfused or receive erythropoietic treatment to meet this criterion.

AST and ALT  $\leq 2.5 \times ULN$ , with the following exception:

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

Serum bilirubin  $\leq 1.5 \times ULN$  with the following exception:

Patients with known Gilbert disease: serum bilirubin level  $\leq 3 \times ULN$

Creatinine clearance  $\geq 30$  mL/min (calculated using the Cockcroft-Gault formula)

Serum albumin  $\geq 2.5$  g/dL

For patients not receiving therapeutic anticoagulation: INR or aPTT  $\leq 1.5 \times ULN$  within 14 days prior to initiation of study treatment
- For patients receiving therapeutic anticoagulation: stable anticoagulant regimen
- For men who are not surgically sterile: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as defined below:
  - With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of  $< 1\%$  per year during the treatment period and for at least 3 months after the last dose of enzalutamide. Men must refrain from donating sperm during this same period.
  - With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for 3 months after the last dose of enzalutamide to avoid exposing the embryo.
  - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

#### Exclusion Criteria

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

#### Cancer-specific exclusions

- Prior treatment with enzalutamide or any other newer hormonal androgen receptor inhibitor (e.g., apalutamide, ODM-201)
- Treatment with any approved anti-cancer therapy, including chemotherapy, immunotherapy, radiopharmaceutical or hormonal therapy (with the exception of abiraterone), within 4 weeks prior to initiation of study treatment
  - Palliative radiotherapy for bone metastases or soft tissue lesions should be completed  $> 7$  days prior to baseline imaging.
  - Androgen deprivation therapy (ADT) with a gonadotropin-releasing hormone (GnRH) analog (GnRH agonist or GnRH antagonist) is allowed.
- Treatment with abiraterone within 2 weeks prior to study treatment
- Use of herbal products that may have hormonal anti-prostate cancer activity and/or are known to decrease PSA levels (e.g., saw palmetto) within 4 weeks of enrollment
- Treatment with any other investigational agent or participation in another clinical study with therapeutic intent within 4 weeks prior to initiation of study treatment

- Planned palliative procedures for alleviation of bone pain such as radiation therapy (unless completed > 7 days prior to baseline imaging) and surgery.
  - Symptomatic lesions amenable to palliative radiotherapy (e.g., bone metastases or metastases causing nerve impingement) should be treated prior to initiation of study treatment.
- Structurally unstable bone lesions suggesting impending fracture
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)
  - Patients with indwelling catheters (e.g., PleurX) are allowed.
- Uncontrolled hypercalcemia defined as one or more of the following criteria:
  - Ionized calcium > 1.5 mmol/L
  - Serum calcium > 12 mg/dL
  - Corrected serum calcium greater than ULN (if serum albumin < 4.0 g/dL)
- Known or suspected brain metastasis or active leptomeningeal disease
- Patients with treated epidural lesions and no other epidural progression are allowed.
  - Asymptomatic metastatic lesions whose further growth would likely cause functional deficits or intractable pain (e.g., epidural metastasis that is not presently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to initiation of study treatment.

#### General medical exclusions

- Malignancies other than mCRPC within 5 years prior to initiation of study treatment
  - Patients with malignancies of a negligible risk of metastasis or death (e.g., risk of metastasis or death < 5% at 5 years) are eligible provided they meet all of the following criteria:
    - Malignancy treated with expected curative intent (e.g., adequately treated basal or squamous cell skin cancer)
    - No evidence of recurrence or metastasis by follow-up imaging and any disease-specific tumor markers
- Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction, or cerebrovascular accident within 3 months prior to enrollment, unstable arrhythmia, or unstable angina
  - Patients with a known left ventricular ejection fraction (LVEF) < 40% will be excluded.
  - Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or LVEF 40%–50% must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate. Patients with a history of clinically significant cardiac disease (including anatomic abnormality, coronary artery disease, congestive heart failure, abnormal LVEF, arrhythmia, or abnormal ECG) will be required to undergo a screening echocardiogram.
  - History of clinically significant ventricular dysrhythmias (e.g., ventricular tachycardia, ventricular fibrillation, torsades de pointes)
  - History of a Mobitz II second degree or third degree heart block without permanent pacemaker in place
  - Hypotension (systolic blood pressure < 86 mmHg) or bradycardia with a heart rate < 50 beats per minute at the screening visit
  - Uncontrolled hypertension as indicated by a resting systolic blood pressure > 170 mmHg or diastolic blood pressure > 105 mmHg at the screening visit
- Major surgical procedure other than for diagnosis within 4 weeks prior to initiation of study treatment or anticipation of need for a major surgical procedure during the course of the study

- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications

Exclusion criteria related to atezolizumab

- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation
- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, or multiple sclerosis, with the following exceptions:

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

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

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

Rash must cover < 10% of body surface area

Disease is well controlled at baseline and requires only low-potency topical corticosteroids

No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months

- Prior allogeneic stem cell or solid organ transplantation
- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan
  - History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Positive HIV test at screening
- Active hepatitis B virus (HBV) infection (chronic or acute), defined as having a positive hepatitis B surface antigen (HBsAg) test at screening
  - Patients with a past or resolved HBV infection, defined as having a negative HBsAg test and a positive total hepatitis B core antibody (HBcAb) test at screening, are eligible for the study.
- Active hepatitis C virus (HCV) infection, defined as having a positive HCV antibody test followed by a positive HCV RNA test at screening
  - The HCV RNA test will be performed only for patients who have a positive HCV antibody test.
- Active tuberculosis
- Severe infection within 4 weeks prior to initiation of study treatment including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia
- Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment

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

- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment or anticipation of need for such a vaccine during the course of the study
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti-CTLA-4, anti-programmed death-1 (PD-1), and anti-PD-L1 therapeutic antibodies
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2) within 4 weeks or five half-lives of the drug, whichever is shorter, prior to initiation of study treatment
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [TNF]- $\alpha$  agents) within 2 weeks prior to initiation of study treatment or anticipation of need for systemic immunosuppressive medication during the course of the study, with the following exceptions:

Patients who received acute, low-dose, systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for in the study.

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

The use of systemic corticosteroids of no greater than the equivalent of 10 mg of prednisone or prednisolone per day for symptomatic treatment of prostate cancer is allowed if the patient has been on a stable dose within 2 weeks prior to initiation of study treatment. There should be no plans to taper the patient off treatment or increase the dose during the study.

Patients who are tapered off systemic corticosteroids as part of a prior anti-cancer regimen must have received the last dose  $\geq 7$  days prior to initiation of study treatment.

#### Exclusion criteria related to enzalutamide

- Known allergy or hypersensitivity to components of the enzalutamide formulation
- Unable to swallow the study treatment
- Gastrointestinal disorder affecting absorption of study treatment (e.g., gastrectomy or active peptic ulcer disease within last 3 months)
- History of seizure or any condition that may predispose to seizure within 12 months prior to study treatment, including unexplained loss of consciousness or transient ischemic attack

#### Exclusion criteria unique to patients enrolled in the enzalutamide PK cohort

- Have used or plan to use the following substances within 30 days or 5 half-lives, whichever is longer, prior to initiation of study treatment through collection of the last enzalutamide PK sample:

Potent CYP2C8 and CYP3A4 inhibitors including, but not limited to, the following: boceprevir, clarithromycin, conivaptan, gemfibrozil, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole

Potent or moderate CYP3A4 and CYP2C8 inducers including, but not limited to, the following: anticonvulsants (carbamazepine, phenobarbital, phenytoin), antimycobacterials (rifabutin, rifampin, rifapentine), avasimibe, bosentan, efavirenz, etavirine, modafinil, nafcillin, St John's wort (*hypericum perforatum*)

#### **End of Study**

The end of the main global study phase is defined as the earliest date of the following:

- Receipt of last data point from the last patient
- Sponsor decision to end the study

## **Length of Study**

The Sponsor has decided to close Study CO39385 (IMbassador250) following the recommendation of the iDMC to terminate the trial due to futility.

## **Investigational Medicinal Products**

The investigational medicinal products (IMPs) for this study are atezolizumab and enzalutamide. The dose level of atezolizumab proposed to be tested in this study is 1200 mg (equivalent to an average body weight-based dose of 15 mg/kg) administered by IV infusion every 3 weeks (21 [ $\pm$  3] days). The dose of enzalutamide is 160 mg (four 40-mg capsules) administered orally once daily.

## **Statistical Methods**

### **Primary Analysis**

The primary efficacy endpoint is overall survival (OS), defined as the time from randomization to death from any cause. Data for patients who are not reported as having died at the date of analysis will be censored at the last date known to be alive. Data for patients who do not have post-baseline information will be censored at the date of randomization plus 1 day.

The intent-to-treat (ITT) population is defined as all randomized patients regardless of whether the assigned study treatment was received. For efficacy analyses, patients will be analyzed according to their randomized treatment assignment.

The primary comparison of OS between treatment arms will be based on a stratified log-rank test. The HR for death in the experimental arm compared with the control arm will be estimated using a stratified Cox regression model, and the 95% CI will be provided. The stratification factors will be the same as the randomization stratification factors; however, stratification factors may be combined for analysis purposes if necessary to minimize small stratum cell sizes. Combination of stratification factors, if any, would be specified in the Statistical Analysis Plan (SAP) prior to analysis. Values for the stratification factors will be as recorded in the IxRS at the time of randomization. Results from an unstratified analysis will also be presented.

Kaplan-Meier plots will be constructed to provide a visual description of the difference between the treatment and control arms. Kaplan-Meier methodology will also be used to estimate median OS for each treatment arm. Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median OS for each treatment arm.

The OS rate at key timepoints (12 months, 24 months) will be estimated using Kaplan-Meier methodology, along with 95% CIs calculated using the standard error derived from Greenwood's formula. The 95% CI for the difference in OS rates between the two treatment arms will be estimated by use of the normal approximation method.

### **Determination of Sample Size**

A total of approximately 730 patients are planned to be enrolled in the global phase of this study: 10 patients during the non-randomized safety run-in phase, and approximately 720 during the randomized phase of the study.

The sample size of 10 patients for the safety run-in is based on clinical considerations. No statistical hypothesis tests will be performed on data from the safety run-in phase.

The final analysis of the primary endpoint of OS will be performed when approximately 540 deaths have occurred in the ITT population (75% of 720 patients).

The calculations are based on the following assumptions:

- Log-rank test
- 1:1 randomization
- Two-sided alpha of 0.05
- Median OS for the control (enzalutamide alone) arm of 12 months and estimated median OS in the experimental arm of 16.7 months, corresponding to a HR of 0.72
- A drop-out rate of approximately 5% per 2-year period
- One interim OS analysis

It is projected that an observed HR of  $\leq 0.84$  will result in a statistically significant difference between treatment arms (i.e., the HR of 0.84 will be the minimally detectable difference at the



final analysis). This corresponds to an improvement of median OS from 12 months to 14.3 months.

In case of proportional hazards, 540 events would provide 97% power to detect a difference in the duration of OS given the above assumptions. However, computer simulations show that the actual power of the log-rank test is likely lower in case of control patients switching to subsequent lines of immunotherapy following progression. For example, if 15% of control patients receive subsequent treatment providing similar OS benefit as atezolizumab, the reduction in power is projected to be approximately 6%.

Recruitment of the planned 720 patients is projected to be completed within 13 months. On the basis of the above assumptions, the required number of OS events for the final analysis is projected to occur at approximately Month 38 after randomizing the first patient.

### **Interim Analyses**

A total of two analyses of OS will be performed: one interim analysis and the final analysis.

The interim analysis of the primary endpoint of OS will be performed when approximately 432 deaths have occurred (60% of 720 patients), corresponding to approximately 80% of the 540 deaths required for the final analysis of OS. The required number of deaths for the interim analysis is projected to occur at approximately Month 27 after randomizing the first patient.

The Lan-DeMets alpha-spending function approach will be used to determine the boundary values for statistical significance at the interim and final analysis.

For the primary endpoint of OS, the stopping boundaries will be based on the O'Brien-Fleming alpha-spending function. At both the interim and final OS analysis, key secondary endpoints listed in Section 6.4.2 will be evaluated for statistical significance only if the difference in duration of OS is statistically significant at the appropriate boundary level. For these secondary endpoints, the boundaries for statistical significance will be based on a Pocock alpha-spending function. Key secondary endpoints will be tested at the appropriate significance level in the order specified in Section 6.4.2. If for one endpoint in this list the null hypothesis cannot be rejected, then the results for this and all following endpoints are not statistically significant.

The hierarchical testing procedure with the boundaries determined as described above ensures that the overall type I error for the primary and key secondary endpoints will be controlled at 0.05.

The interim OS analysis will be performed by the iDCC and reviewed by the iDMC. The Sponsor will remain blinded to the results. On the basis of its review of the data, the iDMC will provide a recommendation as to whether to release the study results early because of substantial evidence of efficacy.

### **Optional Interim Analyses**

To adapt to information that may emerge during the course of this study, the Sponsor may choose to conduct one interim efficacy analysis for the primary endpoint of OS beyond what is specified in Section 6.8.1. The decision to conduct the optional interim analysis, along with the rationale, timing, and statistical details for the analysis, will be documented in the SAP, and the SAP will be submitted to relevant health authorities at least 2 months prior to the conduct of the interim analysis.

If an interim analysis is conducted, the Sponsor will remain blinded. The interim analysis will be conducted by the iDCC and reviewed by the iDMC. Interactions between the iDMC and Sponsor will be carried out as specified in the iDMC Charter.

If there is a potential for the study to be stopped for positive efficacy as a result of the interim analysis, the type I error rate will be controlled using the same Lan-DeMets approach as for the planned interim analysis described above.

## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADT	androgen deprivation therapy
AQA	analgesic quantification algorithm
ATA	anti-therapeutic antibody
BPI, BPI-SF	Brief Pain Inventory, Brief Pain Inventory-Short Form
CI	confidence interval
COPD	chronic obstructive pulmonary disorder
CR	complete response
CRPC	castration-resistant prostate cancer
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DOR	duration of response
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire Core Module 30 items
ePRO	electronic patient-reported outcome
EQ-5D-5L	European Quality-of-Life 5-Dimension Questionnaire
FDA	(U.S.) Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
GHS	global health status
GnRH	gonadotropin-releasing hormone
HRQoL	health-related quality-of-life
HR	hazard ratio
HSPC	hormone-sensitive prostate cancer
IC	(tumor-infiltrating) immune cell
ICH	International Conference for Harmonisation
iDCC	independent Data Coordinating Center
iDMC	independent Data Monitoring Committee
IRF	Independent Review Facility
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IxRS	interactive voice/Web Response System
mCRPC	metastatic castration-resistant prostate cancer
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute

Abbreviation	Definition
NGS	next-generation sequencing
NRS	numerical rating scale
ORR	objective response rate
OS	overall survival
PCWG3	Prostate Cancer Working Group 3
PD-1	programmed death-1
PD-L1	programmed death-ligand 1
PF	physical function
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PRES	posterior reversible encephalopathy syndrome
PRO	patient-reported outcome
PRO-CTCAE	Patient-Reported Outcome version of the Common Terminology Criteria for Adverse Events
PSA	prostate-specific antigen
Q3W	every 3 weeks
QLQ-PR25	EORTC Quality-of-Life Questionnaire Prostate Module 25 items: Urinary Scale
QoL	quality of life
RBR	Research Biosample Repository
RECIST	Response Evaluation Criteria in Solid Tumors
rPFS	radiographic progression-free survival
SAP	Statistical Analysis Plan
SSE	symptomatic skeletal event
TC	tumor cell
TNF(- $\alpha$ )	tumor necrosis factor(- $\alpha$ )
ULN	upper limit of normal
WGS	whole genome sequencing

## **1. BACKGROUND**

### **1.1 BACKGROUND ON PROSTATE CANCER**

With approximately 1.1 million newly diagnosed cases and more than 300,000 deaths each year worldwide, prostate cancer is the most commonly diagnosed cancer in men and the second leading cause of death in men in the Western world (Ferlay et al. 2013). The incidence rates are highest in developed regions, including North America (approximately 180,000 new cases and 26,000 deaths in the United States in 2016), Europe (approximately 70,000 deaths in 2013), and Australia/New Zealand (Malvezzi et al. 2013; Ferlay et al. 2013; Siegel et al. 2016). Whereas most men with localized disease are cured with treatment, men with recurrent or newly diagnosed metastatic disease suffer significant morbidity and mortality (Kirby et al. 2011).

For patients who have recurrence following localized treatment and for those patients identified with de novo metastatic disease, the goal of treatment is to extend survival while maintaining health-related quality of life (HRQoL). Primary treatment is androgen deprivation therapy (ADT); however, up to one-third of patients will progress despite reduction in testosterone levels to castrate levels (<50 ng/dL) either through surgical or medical castration (Kirby et al. 2011). Castration-resistant prostate cancer (CRPC) is defined by disease progression, as measured by prostate-specific antigen (PSA) or radiographic measures despite adequate suppression of testosterone levels (Prostate Cancer Working Group 3 [PCWG3]; Scher et al. 2016). Despite the current availability of life-extending therapies for metastatic CRPC (mCRPC), the majority of men will experience deterioration in HRQoL, disability and ultimately die of their disease (Kirby et al. 2011; Logothetis et al. 2012; Basch et al. 2014; Fizazi et al. 2014). Up to 90% of patients with mCRPC develop bone metastasis, complications for which include severe pain, pathologic fractures, life-threatening hypercalcemia, spinal cord compression, and other nerve-compression syndromes (Roodman et al. 2004; Pezaro et al. 2013). The median life expectancy in patients diagnosed with mCRPC is less than three years and less than one year in patients who have failed two prior lines of therapy (Ryan et al. 2013; Beer et al. 2014; Roviello et al. 2015). Overall, there is still a significant unmet medical need in this patient population.

#### **1.1.1 Current Therapies for Metastatic Prostate Cancer**

The number of treatment options for patients with metastatic prostate cancer have increased in the last decade, and paradigms have shifted to the earlier use of active agents (Parker et al. 2015; Mohler et al. 2016). Docetaxel, a cytotoxic chemotherapy and microtubule inhibitor, was initially evaluated in combination with estramustine or prednisone in the castration-resistant setting and showed an improvement in median overall survival (OS) of approximately 2 months compared with mitoxantrone and prednisone (HR=0.80; 95% confidence interval [CI]: 0.67, 0.97; p=0.02, Petrylak et al. 2004; HR=0.76; 95% CI: 0.62–0.94; p=0.009, Tannock et al. 2004). Grade 3 and 4 neutropenic fevers, nausea and vomiting, cardiovascular events, metabolic disturbances and neurologic events, including sensory neuropathy, were more

common in the groups that received docetaxel. More recently, docetaxel was evaluated in the hormone-sensitive prostate cancer (HSPC) setting (also referred to as castration-naive setting), with two studies demonstrating statistically significant and clinically meaningful improvements in OS when combined with initiation of ADT for newly diagnosed metastatic disease (Sweeney et al. 2015; James et al. 2016). Docetaxel plus ADT is now accepted as a standard-of-care treatment option for patients with HSPC with clinically measurable disease in appropriately selected patients (Parker et al. 2015; Mohler et al. 2016).

Subsequent to the approval of docetaxel in mCRPC, five drugs were approved for the treatment of mCRPC, including sipuleucel-T, cabazitaxel, abiraterone, enzalutamide, and radium-223 dichloride.

Sipuleucel-T, an autologous active cellular immunotherapy, demonstrated a 4.1-month improvement in median survival (HR=0.78; 95% CI: 0.61, 0.98; p=0.03). The time to radiographic and clinical disease progression was similar in the two study groups; one patient in the sipuleucel-T group had a partial response (PR) and PSA responses were low in both study groups. Adverse events that were more frequently reported in the sipuleucel-T group than in the placebo group included chills, fever, and headache, with Grade 3 and 4 events reported in 6.8% versus 1.8% of patients in the sipuleucel-T and placebo group, respectively. Sipuleucel-T is the only immunotherapy currently approved for prostate cancer (limited to the United States) for use in patients with minimal or no symptoms (Kantoff et al. 2010).

Cabazitaxel is a novel microtubule inhibitor and, in combination with prednisone, was compared to mitoxantrone in combination with prednisone in patients in the post-docetaxel setting (de Bono et al. 2010). A statistically significant improvement in the primary endpoint of OS was demonstrated (median OS: 15.1 vs. 12.7 months; HR=0.70; 95% CI: 0.59, 0.83; p<0.0001). Key secondary endpoints were similarly improved, including radiographic progression-free survival (rPFS) and time to PSA progression; there was no significant difference between the treatment groups in time to pain progression. The most common clinically significant Grade 3 and 4 adverse events in the cabazitaxel group were neutropenia (including febrile neutropenia) and diarrhea.

Abiraterone is an inhibitor of the enzyme cytochrome P450 17A1 (CYP17 $\alpha$ : 17 $\alpha$ -hydroxylase/C17, 20-lyase). Abiraterone acts as an androgen synthesis inhibitor by blocking two enzymatic activities in the synthesis of testosterone in the testes, adrenals, and within the prostate tumor (Li et al. 2015). Abiraterone in combination with prednisone was initially compared to prednisone alone in the post-docetaxel setting, and statistically significant improvement was demonstrated with the primary endpoint of OS when assessed at interim analysis (median OS: 14.8 vs. 10.9 months; HR=0.646; 95% CI: 0.543, 0.768; p<0.0001; de Bono et al. 2011). Supportive secondary endpoints included rPFS and time to PSA progression, as well as, pain-related endpoints, including time to pain severity and time to pain interference progression, pain severity palliation,

skeletal-related events, as well as improvement in prostate-related symptoms including fatigue and HRQoL (de Bono et al. 2011; Logothetis et al. 2012; Harland et al. 2013; Sternberg et al. 2013). In the pre-docetaxel setting in asymptomatic and mildly symptomatic patients, abiraterone and prednisone was again compared with prednisone alone; rPFS and OS were assessed as co-primary endpoints. At interim analysis, the study demonstrated statistically significant improvement in rPFS as assessed by independent radiographic review (Ryan et al. 2013) with a trend in OS (third interim analysis; median; 35.3 vs. 30.1 months; HR=0.792;  $p < 0.0151$  [did not cross statistical boundaries for early stopping]). As with the post-docetaxel study, supportive secondary endpoints included delay in opiate use for prostate cancer pain, initiation of cytotoxic chemotherapy, deterioration in Eastern Cooperative Oncology Group (ECOG) performance status, and PSA progression (Basch et al. 2013). Grade 3 or 4 mineralocorticoid-related adverse events, including fluid retention, hypertension and hypokalemia, and abnormalities in liver function were more common with the abiraterone and prednisone combination in both studies.

More recently, abiraterone and prednisone/prednisolone were evaluated in the HSPC setting, with two studies demonstrating statistically significant and clinically meaningful improvements in OS when combined with ADT (Fizazi et al. 2017; James et al. 2017). The LATITUDE study compared ADT plus abiraterone and prednisone with ADT plus placebo in patients with metastatic HSPC, and a statistically significant improvement was demonstrated with the primary endpoints of OS (HR=0.62;  $p < 0.001$ ) and progression-free survival (PFS) (median: 33.0 months vs. 14.8 months; HR=0.47;  $p < 0.001$  [Fizazi et al. 2017]). The STAMPEDE study compared ADT plus abiraterone and prednisolone with ADT alone in patients with HSPC, and statistically significant improvement was demonstrated for the primary outcome of OS (HR=0.63;  $p < 0.001$ ) and the intermediate primary outcome of failure-free survival (HR=0.29;  $p < 0.001$ ) (James et al. 2017).

Enzalutamide is an oral androgen receptor blocker that impacts receptor signaling at multiple steps, including competitive binding to the androgen receptor, inhibition of nuclear translocation, and consequently prevention of binding of the androgen receptor to relevant activation sequences in the nucleus. Enzalutamide demonstrated statistically significant improvement over placebo in the primary endpoint of OS in the post-docetaxel setting in mCRPC patients (18.4 vs. 13.6 months; HR=0.631,  $p < 0.0001$ ). Additionally, key secondary endpoints demonstrated statistically significant differences including rPFS, time to first skeletal-related event, and time to PSA progression (Scher et al. 2012). In a second pivotal study in the pre-docetaxel setting in asymptomatic and mildly symptomatic patients, enzalutamide demonstrated statistically significant improvement over placebo in the co-primary endpoints of rPFS (not yet reached vs. 3.9 months; HR=0.186;  $p < 0.0001$ ) and OS (32.4 vs. 30.2 months; HR=0.706;  $p < 0.0001$  [Beer et al. 2014]). Other key secondary endpoints, which supported the rPFS and OS data, included time to first skeletal-related event, time to

initiation of cytotoxic chemotherapy, and time to PSA progression. Rates of fatigue and hypertension were higher in the enzalutamide groups in both studies. Seizures were reported in less than 1% of patients receiving enzalutamide.

Radium-223 dichloride is an alpha-emitting calcium mimetic radioisotope, which localizes to bone forming regions of cancer metastases (Parker et al. 2013). It is an applicable treatment for symptomatic patients without visceral disease. Radium-223 was compared to placebo in patients with symptomatic mCRPC with bone-only disease and demonstrated significant improvement in the primary endpoint of OS (14.9 vs. 11.3 months; HR=0.70;  $p < 0.001$ ); additionally, the key secondary endpoint of time to first symptomatic skeletal-related event was similarly improved (15.6 vs. 9.8 months; HR=0.66;  $p < 0.001$ ). Radium-223 dichloride was associated with low myelosuppression rates and fewer adverse events than the placebo group.

Despite recent advances in the treatment of prostate cancer described above, patients with mCRPC experience significant morbidity and mortality related to their disease and the median life expectancy from time of first metastatic diagnosis remains less than 3 years.

### **1.1.2 Treatment Patterns for Metastatic Prostate Cancer**

With the approval of the aforementioned agents for metastatic prostate cancer, physicians now have several treatment options available. In the context of incurable metastatic disease, practice guidelines in the United States and European Union agree that the goal of treatment is to provide the best possible quality of life for as long as possible (Basch et al. 2014; Heidenreich et al. 2014; Parker et al. 2015; Mohler et al. 2016). Consequently, they generally consider hormonal-based therapies as appropriate first-line treatment for patients with asymptomatic or mildly (or “minimally”) symptomatic disease, whereas patients with symptomatic disease or disease refractory to hormonal agents should be treated with cytotoxic chemotherapy. However, there is limited data to define the appropriate sequence to optimize outcomes for patients and no expert consensus exists for the best sequencing of agents. In the absence of data informing the best treatment sequence in prostate cancer, the choice between hormonal treatment and taxane-based chemotherapy after prior treatment failure remains unclear. Clinical practice guidelines in the United States and European Union generally do not recommend a preferred next treatment option, and enzalutamide and abiraterone can be given to patients not previously treated with the other drug (Basch et al. 2014; Heidenreich et al. 2014; Parker et al. 2015; Mohler et al. 2016).

Although options exist for mCRPC, the magnitude of benefit in patients treated with a hormonally-based therapy may be attenuated after a taxane-containing therapy and vice versa (de Bono et al. 2011; Scher et al. 2012; Ryan et al. 2013; Beer et al. 2014), possibly partly due to a cross-resistance mechanism in which microtubule inhibition may alter translocation of the androgen receptor (van Soest et al. 2013).

Furthermore, gene aberrations in the androgen receptor and the presence of androgen receptor splice variants may also contribute to impaired clinical efficacy when abiraterone and enzalutamide are used sequentially (Antonarakis et al. 2014; Azad et al. 2015; Romanel et al. 2015). Consequently, outcomes in patients who have failed two prior lines of therapy remain poor with response rates of approximately 10%–15%, PFS of approximately 3 months, and an OS of less than one year (Caffo et al. 2015; Roviello et al. 2015).

However, enzalutamide has demonstrated anti-tumor activity in mCRPC patients previously treated with abiraterone. A recent prospective Phase IV, open-label study evaluated the efficacy and safety of enzalutamide in patients with mCRPC who had progressed after at least 24 weeks of abiraterone and prednisone treatment. In this study, enzalutamide demonstrated anti-tumor activity with an rPFS of 8.1 months, a PSA response rate of 26.5%, and a median time to PSA progression of 5.7 months (de Bono et al. 2017).

Despite a proven survival benefit, the overall use of docetaxel-based chemotherapy in patients with mCRPC remains low due to concerns about tolerability and patient preference not to receive chemotherapy. Population-based studies from Sweden and the United Kingdom suggest that only approximately 20% of patients who die from prostate cancer had received docetaxel, with significantly higher treatment rates among younger patients and patients with fewer comorbidities (Harris et al. 2011; Lissbrant et al. 2013). Additional studies of treatment patterns conducted in the United States describe docetaxel treatment rates of approximately 40%, and 16% in the elderly (Onukwugha et al. 2011; Lafeuille et al. 2013).

Given the above limitations of current treatments available for patients, improved and tolerable treatment options following initial treatment with a newer hormonal agent are needed.

## **1.2 BACKGROUND ON ATEZOLIZUMAB**

Atezolizumab (TECENTRIQ®), formerly known as MPDL3280A, is a humanized IgG1 MAbs consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids) and is produced in Chinese hamster ovary cells. It targets programmed death ligand-1 (PD-L1) and inhibits the interaction between PD-L1 and its receptors, programmed death-1 (PD-1) and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to Fc $\gamma$  receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.



Atezolizumab shows anti-tumor activity in both nonclinical models and patients with cancer and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy.

Atezolizumab is approved in the United States for the treatment of locally advanced or metastatic urothelial carcinoma.

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

### **1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT**

#### **1.3.1 Rationale for Treatment with Atezolizumab**

Encouraging clinical data emerging in the field of tumor immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant clinical benefit to patients across a broad array of advanced malignancies (Hodi et al. 2010; Kantoff et al. 2010; Chen et al. 2012).

The PD-L1 pathway serves as an immune checkpoint to temporarily dampen immune responses in states of chronic antigen stimulation, such as chronic infection or cancer. PD-L1 is an extracellular protein that downregulates immune responses through binding to its two receptors, PD-1 and B7-1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, and expression is sustained in states of chronic stimulation (Blank et al. 2005; Keir et al. 2008). B7-1 is a molecule expressed on antigen-presenting cells and activated T cells. Binding of PD-L1 to PD-1 and B7-1 inhibits T-cell proliferation and activation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells (Butte et al. 2007; Yang et al. 2011). Overexpression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion (Blank and Mackensen 2007). Therefore, interruption of the PD-L1 pathway represents an attractive strategy for restoring tumor-specific T-cell immunity.

In prostate cancer, a study evaluating PD-L1 expression in primary tissue at the time of radical prostatectomy demonstrated moderate to high PD-L1 expression in 61.7% of resection specimens; PD-L1 expression was prognostic for biochemical recurrence (Gevensleben et al. 2016). Similarly, PD-L1 expression was detected in 50% of prostate adenocarcinomas in a different data set, with 19% of cases showing high positivity (2+ score; Massari et al. 2016). A study evaluating PD-L1 expression on immune cells (ICs) in the tumor area using the Ventana/Roche anti-PD-L1 (SP142) assay on prostate cancer tissue from 92 patients detected PD-L1 expression on tumor-infiltrating ICs in 39% of the samples (defined as > 1% PD-L1 expression on tumor-infiltrating ICs). PD-L1 expression on tumor cells was limited to 2% of the samples (defined as > 1% PD-L1 expression on tumor cells; unpublished data).

Targeting the PD-L1 pathway with atezolizumab has demonstrated activity in patients with advanced malignancies who have failed standard-of-care therapies. Objective responses have been observed across a broad range of malignancies, including non–small cell lung cancer (NSCLC), urothelial carcinoma, renal cell carcinoma (RCC), melanoma, colorectal cancer, head and neck cancer, gastric cancer, breast cancer, and sarcoma (see Atezolizumab Investigator's Brochure for detailed efficacy results).

Atezolizumab has been generally well tolerated. Adverse events with potentially immune-*mediated* causes consistent with an immunotherapeutic agent, including rash, influenza-like illness, endocrinopathies, hepatitis or transaminitis, pneumonitis, colitis, and myasthenia gravis, have been observed (see Atezolizumab Investigator's Brochure for detailed safety results). To date, these events have been manageable with treatment.

### **1.3.2 Rationale for Combination Treatment with Atezolizumab and Enzalutamide**

Hormonal therapies have been shown to have several immune modulatory effects, including the promotion of thymopoiesis, an increase in prostate immune infiltrate, and inhibition of tolerance to prostatic antigens (Schweizer et al. 2014).

#### **1.3.2.1 Androgen Deprivation Therapy**

Nonclinical data describing restoration of thymic architecture, normalization of thymocyte differentiation, proliferation and increase in peripheral naive T cells in surgically castrated mice have recently been corroborated by similar findings in humans (Sutherland et al. 2005). In addition, androgen ablation therapy induced T-cell infiltration of prostate cancer tissue, induced prostate-specific humoral immune responses and increased T-cell proliferative responsiveness in patients (Mercader et al. 2001; Roden et al. 2004; Nesslinger et al. 2007; Gannon et al. 2009; Morse et al. 2010).

In mouse models, the presence of invasive prostate cancer leads to prostate antigen recognition by T cells and subsequent development of immune tolerance. Androgen ablation therapy administered in the presence of prostate cancer reversed this acquired immune tolerance (Drake et al. 2005; Arredouani et al. 2010). Similarly, castration-enhanced antigen specific IFN- $\gamma$  production after vaccination and castrated mice had elevated IL-2 and IFN- $\gamma$  production capacity compared to sham-castrated mice (Viselli et al. 1995; Koh et al. 2009).

#### **1.3.2.2 Enzalutamide**

Enzalutamide is a modern anti-androgen therapy and has only recently been studied with regard to its immune modulatory properties. Similar to ADT, murine and human data demonstrated that enzalutamide enhances thymic production of naive T cells (Ardiani et al. 2013; Donahue et al. 2016). Other immune activating properties described in humans include, but are not limited to, an increase in natural killer cells, a decrease in myeloid derived suppressor cells, and an increased activation of IFN- $\gamma$  signaling in peripheral blood mononuclear cells (Donahue et al. 2016). Preliminary

clinical data of enzalutamide in combination with a PD-1-inhibitor, pembrolizumab, showed almost complete PSA responses in three out of ten patients who had previously failed enzalutamide or abiraterone and enzalutamide (Graff et al. 2016). Two of these 3 patients had measurable disease at study entry; both achieved a PR.

Murine studies further suggest that enzalutamide sensitizes tumor cells to cytotoxic T- cell mediated lysis and promotes tumor apoptosis, which may lead to an increase in tumor-associated antigens and antigen presentation (Guerrero et al. 2013; Ardiani et al. 2013). Moreover, a combination of enzalutamide with a vaccine improved survival in mice compared to no treatment, vaccine alone, and enzalutamide alone (Ardiani et al. 2013; Kwilas et al. 2015).

In summary, these clinical and nonclinical data support combining enzalutamide and immunotherapy, with enzalutamide hypothesized to serve as an immune adjuvant.

### **1.3.2.3      Atezolizumab Tolerability Profile during Combination Treatment**

In studies investigating the combination of atezolizumab with other anti-cancer agents, the incidence of adverse events in the treatment arms with combined use was consistent with the known safety profiles of the individual study drugs. Fatigue, decreased appetite, nausea and cough were adverse events reported in more than 10% of patients treated with atezolizumab monotherapy and in combination therapy. Through appropriate routine evaluations, investigational workup, and early mitigations such as management guidelines, the majority of patients were able to continue atezolizumab therapy (see Atezolizumab Investigator's Brochure for detailed safety results).

In summary, the immune modulatory properties of hormonal therapy and especially enzalutamide, the tolerability of atezolizumab when given in combination therapy and the unmet need in the proposed patient population, provide a rationale for the proposed study. This treatment strategy could provide a meaningful clinical benefit to patients with mCRPC with a manageable tolerability profile.

### **1.3.3              Benefit-Risk Assessment**

This study will enroll patients with mCRPC after failure of an androgen synthesis inhibitor (e.g., abiraterone) and failure of, ineligibility for, or refusal of a taxane regimen. Given the relatively poor prognosis and limited treatment options for these patients, this population is considered appropriate for studies of novel therapeutic candidates. Patients in both treatment arms will receive a standard-of-care treatment, (i.e., enzalutamide). The benefit-risk ratio for atezolizumab in combination with enzalutamide versus enzalutamide alone is expected to be acceptable in this setting.

## **2.                      OBJECTIVES AND ENDPOINTS**

This is a Phase III, multicenter, randomized open-label study designed to evaluate the efficacy and safety of atezolizumab in combination with enzalutamide compared with

enzalutamide alone in patients with mCRPC after failure of an androgen synthesis inhibitor and failure of, ineligibility for, or refusal of a taxane regimen. Specific objectives and corresponding endpoints for the study are outlined in [Table 1](#).

**Table 1 Objectives and Corresponding Endpoints**

<b>Primary Efficacy Objective</b>	<b>Corresponding Endpoint</b>
<ul style="list-style-type: none"> <li>•To evaluate the efficacy of atezolizumab/enzalutamide compared with enzalutamide alone</li> </ul>	<ul style="list-style-type: none"> <li>•OS, defined as the time from randomization to death from any cause</li> </ul>
<b>Country-Specific Objective for China</b>	<b>Corresponding Endpoint</b>
<ul style="list-style-type: none"> <li>•To evaluate the efficacy of atezolizumab/enzalutamide compared with enzalutamide alone in patients who are residents of China</li> </ul>	<ul style="list-style-type: none"> <li>•Same as the primary objective</li> </ul>
<b>Secondary Efficacy Objective</b>	<b>Corresponding Endpoints</b>
<ul style="list-style-type: none"> <li>•To evaluate the efficacy of atezolizumab/enzalutamide compared with enzalutamide alone</li> </ul>	<ul style="list-style-type: none"> <li>•OS probability at 12 and 24 months</li> <li>•Time to first SSE An SSE is defined as external beam radiation therapy to relieve skeletal symptoms (including initiation of radium-223 dichloride or other types of radionuclide therapy to treat symptoms of bone metastases), new symptomatic pathologic bone fracture, clinically apparent occurrence of spinal cord compression, or tumor related orthopedic surgical intervention.</li> <li>•rPFS, as assessed by the investigator, and adapted from the PCWG3 criteria (Scher et al. 2016; see <a href="#">Appendix 2</a>). rPFS is defined as the time from randomization to the earliest occurrence of one of the following: A patient is considered to have progressed by bone scan if: The first bone scan with <math>\geq 2</math> new lesions compared to baseline is observed <math>&lt; 12</math> weeks from randomization and is confirmed by a second bone scan taken <math>\geq 6</math> weeks later showing <math>\geq 2</math> additional new lesions (a total of <math>\geq 4</math> new lesions compared to baseline); the date of progression is the date of the first post-treatment scan, OR After the first post-treatment scan, <math>\geq 2</math> new lesions are observed relative to the first post-treatment scan, which is confirmed on a subsequent scan <math>\geq 6</math> weeks later; the date of progression is the date of the post-treatment scan when <math>\geq 2</math> new lesions were first documented.</li> <li>Progression of soft tissue lesions, as defined per PCWG3 modified RECIST v1.1</li> <li>Death from any cause</li> </ul>

**Table 1 Objectives and Corresponding Endpoints (cont.)**

Secondary Efficacy Objective (cont.)	Corresponding Endpoints
To evaluate the efficacy of atezolizumab/enzalutamide compared with enzalutamide alone (cont.)	<ul style="list-style-type: none"> <li>• rPFS probability at 6 and 12 months</li> <li>• PSA response rate, defined as a &gt; 50% decrease in PSA from baseline that is confirmed after ≥ 3 weeks by a consecutive confirmatory PSA measurement</li> <li>• Time to PSA progression, defined as the time from randomization to the time of PSA progression, as defined per the PCWG3 criteria (Scher et al. 2016): <ul style="list-style-type: none"> <li>In patients with no PSA decline from baseline, PSA progression is defined as a ≥ 25% increase and an absolute increase of ≥ 2 ng/mL above the baseline value, ≥ 12 weeks after baseline.</li> <li>In patients with an initial PSA decline from baseline, PSA progression is defined as a ≥ 25% increase and an absolute increase of ≥ 2 ng/mL above the nadir value, which is confirmed by a consecutive second value obtained ≥ 3 weeks later.</li> </ul> </li> <li>• Objective response rate in soft tissue lesions, defined as the proportion of patients with either a CR or PR on two consecutive occasions ≥ 6 weeks apart, as determined by the investigator through use of PCWG3 criteria (see <a href="#">Appendix 2</a>)</li> </ul>
Exploratory Efficacy Objective	Corresponding Endpoints
• To evaluate the efficacy of atezolizumab/enzalutamide compared with enzalutamide alone	<ul style="list-style-type: none"> <li>• DOR in soft tissue lesions, defined for patients who had an objective response in soft tissue as the time from the first documented objective response in soft tissue to radiographic disease progression, as determined by the investigator through use of PCWG3 criteria</li> <li>• DCR, defined as the proportion of patients with a best response of confirmed CR or PR or stable disease in soft tissue lesions per PCWG3-modified RECIST v1.1 and/or no confirmed radiographic disease progression on bone scan per PCWG3 criteria (see <a href="#">Appendix 2</a>)</li> <li>• Modified progression free survival based on radiographic disease progression and unequivocal clinical progression, defined as the time from randomization to the earliest occurrence of one of the following: <ul style="list-style-type: none"> <li>Radiographic disease progression per PCWG3 criteria (as defined above)</li> <li>Unequivocal clinical progression characterized as at least one of the following: <ul style="list-style-type: none"> <li>Symptomatic skeletal-related event (as defined above)</li> <li>Deterioration in ECOG performance status by at least two points that is attributed to disease progression</li> <li>Initiation of next systemic anti-cancer therapy</li> </ul> </li> </ul> </li> </ul>

**Table 1 Objectives and Corresponding Endpoints (cont.)**

<b>Safety Objective</b>	<b>Corresponding Endpoints</b>
<ul style="list-style-type: none"> <li>•To evaluate the safety and tolerability of atezolizumab and enzalutamide compared with enzalutamide alone</li> </ul>	<ul style="list-style-type: none"> <li>•Incidence, nature, frequency, and severity of adverse events, with severity determined through use of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v4.0)</li> <li>•Clinically significant changes in vital signs, and clinical laboratory results during and following study treatment administration</li> </ul>
<b>Pharmacokinetic Objectives</b>	<b>Corresponding Endpoints</b>
<ul style="list-style-type: none"> <li>•To characterize the pharmacokinetics of atezolizumab when given in combination with enzalutamide</li> <li>•To characterize the pharmacokinetics of enzalutamide and its active metabolite N-desmethyl enzalutamide when enzalutamide is administered alone or in combination with atezolizumab</li> </ul>	<ul style="list-style-type: none"> <li>•Serum concentration of atezolizumab at specified timepoints</li> <li>•Plasma concentration of enzalutamide and N-desmethyl enzalutamide at specified timepoints in the safety run-in phase and in a PK cohort in the randomized phase (approximately 30 patients per treatment arm)</li> </ul>
<b>Exploratory Biomarker Objective</b>	<b>Corresponding Endpoints</b>
<ul style="list-style-type: none"> <li>•To identify biomarkers that are predictive of response to atezolizumab and/or enzalutamide (i.e., predictive biomarkers), are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to atezolizumab and/or enzalutamide, are associated with susceptibility to developing adverse events, can provide evidence of atezolizumab and/or enzalutamide activity, or can increase the knowledge and understanding of disease biology on the basis of the following endpoint:</li> </ul>	<ul style="list-style-type: none"> <li>•Relationship between biomarkers in blood, urine, and tumor tissue (listed in Section 4.5.6) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints</li> </ul>

**Table 1 Objectives and Corresponding Endpoints (cont.)**

<b>Immunogenicity Objective</b>	<b>Corresponding Endpoint</b>
•To evaluate the immune response to atezolizumab	•Incidence of anti-therapeutic antibodies (ATAs) against atezolizumab
<b>Exploratory Immunogenicity Objective</b>	<b>Corresponding Endpoint</b>
•To evaluate potential effects of ATAs	•Relationship between ATA status and efficacy, safety, or PK endpoints

AQA= analgesic quantification algorithm; ATA= anti-therapeutic antibody; CR= complete response; CRPC= castration-resistant prostate cancer; DCR= disease control rate; DOR= duration of response; ECOG= Eastern Cooperative Oncology Group; NCI CTCAE= National Cancer Institute Common Terminology Criteria for Adverse Events; OS= overall survival; PCWG3= Prostate Cancer Working Group 3; PF= physical function; PFS= progression-free survival; PK= pharmacokinetic; PR= partial response; PSA= prostate-specific antigen; rPFS= radiographic progression-free survival; RECIST= Response Evaluation Criteria in Solid Tumors; SSE= symptomatic skeletal event.

### **3. STUDY DESIGN**

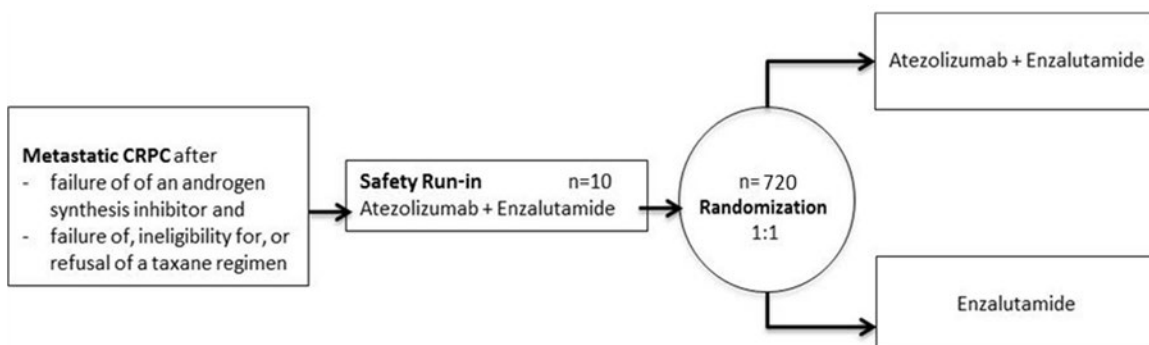
#### **3.1 DESCRIPTION OF THE STUDY**

This is a Phase III, multicenter, randomized, open-label study designed to evaluate the safety and efficacy of atezolizumab in combination with enzalutamide compared with enzalutamide alone in patients with mCRPC after failure of an androgen synthesis inhibitor (e.g., abiraterone) and failure of, ineligibility for, or refusal of a taxane regimen.

Specifically, the study will include the following patients:

- Patients who have progressed during treatment with an androgen synthesis inhibitor (e.g., abiraterone) for prostate cancer and have received a prior taxane regimen for metastatic hormone-sensitive and/or metastatic castration-resistant prostate cancer
- Patients who have progressed during treatment with an androgen synthesis inhibitor (e.g., abiraterone) for prostate cancer and who are not fit enough to receive a taxane regimen for mCRPC
- Patients who have progressed during treatment with an androgen synthesis inhibitor (e.g., abiraterone) for prostate cancer and who decline a taxane regimen for mCRPC after an informed discussion

**Figure 1 Study Schema**



CRPC = castration-resistant prostate cancer; iDMC = independent Data Monitoring Committee.

Notes: Enzalutamide: 160 mg orally per day. Atezolizumab: 1200 mg by IV infusion on Day 1 of each 21-day cycle. Treatment will continue until lack of clinical benefit, worsening of symptoms, decline in performance status, or tumor progression at a critical site that cannot be managed with protocol-accepted therapy. No crossover will be allowed from the control arm to the experimental arm.

Safety run-in phase: Ten patients will be followed for at least 1 cycle (21 days) after which the iDMC will make a recommendation regarding initiating enrollment in the randomized phase of the study. Patients in the safety run-in phase will continue to receive study treatment and be followed for safety and efficacy.

Approximately 180 sites globally will participate in the study and approximately 730 patients will be enrolled (first 10 patients in the safety run-in cohort followed by 720 patients in the global randomized phase).

The Sponsor recommends that investigators use their clinical judgment to determine if the patients who remain on the study appear to be benefitting from their therapy, and discuss the benefits and risks with patients of remaining on their current treatment. Patients who remain on treatment until the closure of the study will be able to continue to receive treatment as part of a post-trial access program. Patients may start transferring to the program after the required approvals are available (as applicable).

### **Safety Run-In Phase**

In the safety run-in phase of the study, 10 patients will be enrolled and will receive atezolizumab in combination with enzalutamide. After 10 patients have been enrolled, enrollment will be stopped temporarily and all patients will be monitored closely for adverse events until the last patient has completed the first cycle (21 days). Patients will continue to receive study treatment and be followed for safety and efficacy per the schedule of activities in [Appendix 1](#).

After 10 patients have received study treatment and completed at least one cycle of study treatment (21 days), an independent Data Monitoring Committee (iDMC) will review available data and make a recommendation regarding initiation of the randomized phase of the study. For further information on the iDMC, see [Section 3.2](#).



## Randomized Phase

Enrollment in the randomized phase of the study will be initiated after review of the safety run-in data by the iDMC and the Sponsor. Approximately 720 patients will be enrolled in the randomized phase of the study. Patients will be randomized to one of the following treatment arms in a 1:1 ratio (experimental to control arm):

- Arm A (experimental arm): atezolizumab in combination with enzalutamide
- Arm B (control arm): enzalutamide alone

Randomization will be conducted with the aid of an interactive voice/Web response system (IxRS).

The randomization will be stratified by the following stratification factors:

- Prior taxane-containing regimen for mCRPC, defined as at least two cycles of a taxane-containing regimen (yes vs. no)
- Presence of liver metastasis (yes vs. no)
- LDH  $\leq$  upper limit of normal (ULN) vs.  $>$  ULN
- Pain severity (BPI-Short Form [SF] Question 3 assessing pain at its worst over the past 24 hours [score  $<$  4 vs.  $\geq$  4]) ([Appendix 7](#))

A stratified permuted-block randomization will be implemented to balance treatment assignment within stratum levels.

Patient recruitment will be capped with respect to two of the stratification factors: the proportion of patients who have not received a prior taxane-containing regimen for mCRPC will be approximately 50% or less, and the proportion of patients with liver metastases at baseline will be approximately 10% or less. Presence of liver metastases will be determined based on CT or MRI scan. The purpose of the cap is to ensure the prevalence of these two prognostic factors in the study population will be similar to that reported in the targeted population.

Atezolizumab will be administered at a fixed dose of 1200 mg by IV infusion on Day 1 of each 21-day cycle until investigator-assessed confirmed radiographic disease progression per PCWG3 or unacceptable toxicity.

Enzalutamide will be administered orally at a dose of 160 mg (four 40-mg capsules) daily until investigator-assessed confirmed radiographic disease progression per PCWG3 or unacceptable toxicity.

Patients will be permitted to continue study treatment after PCWG3 criteria are met for confirmed radiographic disease progression if they meet all of the following criteria (treatment until they are no longer clinically benefiting per PCWG3 recommendation [Scher et al. 2016]).

- Evidence of clinical benefit as assessed by the investigator
- Absence of symptoms and signs indicating unequivocal progression of disease
- No decline in ECOG performance status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed and stabilized by protocol-allowed medical interventions
- Written consent to acknowledge deferring other treatment options in favor of continuing study treatment at the time of initial disease progression

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

Patients with rising PSA levels only (i.e., in the absence of confirmed radiographic or clinical progression) should continue to receive study treatment per PCWG3 criteria and recommendations (Scher et al. 2016). PSA rise without evidence of confirmed radiographic progression or a symptomatic skeletal-related event is strongly discouraged as a criterion to start a new systemic anti-neoplastic therapy during the first 12 weeks of therapy and is discouraged as a criterion to start a new systemic anti-neoplastic therapy throughout the study.

Focal palliative radiography (e.g., external-beam radiotherapy to address single sites of disease), initiation of bisphosphonates or denosumab, standard-of-care corticosteroid use of no greater than the equivalent of 10 mg of prednisone or prednisolone per day and pain management are allowed and should not result in discontinuation of study treatment. However, patients should be evaluated for clinically apparent SSE.

Initiation of radium-223 dichloride to manage symptomatic bone lesions is not permitted during study treatment.

Patients will undergo scheduled tumor assessments at baseline and every 9 weeks ( $\pm 3$  days) for the first 27 weeks and every 12 weeks ( $\pm 6$  days) thereafter until confirmed radiographic disease progression per PCWG3. In the absence of confirmed radiographic progression, tumor assessments should continue, regardless of whether patients start new anti-cancer therapy, until death, loss of follow-up, withdrawal of consent, or study termination by the Sponsor, whichever occurs first. For patients who continue to receive study treatment following confirmed disease progression, assessments will continue until loss of clinical benefit.

All primary imaging data used for tumor assessments may be collected by the Sponsor to enable the possibility of a centralized, independent review of response endpoints by an Independent Review Facility (IRF).

Safety assessments will include the incidence, nature, and severity of adverse events and laboratory abnormalities graded per the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0). Laboratory safety assessments will include the regular monitoring of hematology and blood chemistry.

Serum samples will be collected in patients in Arm A (atezolizumab and enzalutamide) to monitor atezolizumab pharmacokinetics and to detect the presence of antibodies to atezolizumab. Plasma samples to monitor enzalutamide and N-desmethyl enzalutamide pharmacokinetics will also be collected in the safety run-in phase and in a PK cohort in the randomized phase (approximately 30 patients per treatment arm). Patient samples, including archival tumor tissues, as well as urine, serum, plasma and whole blood, will be collected for future exploratory biomarker assessments for all patients in the randomized phase.

It is recommended that patients undergo tumor biopsy sample collection, if deemed clinically feasible by the investigator, at the time of first evidence of confirmed radiographic disease progression according to PCWG3 criteria (within 40 days after confirmed radiographic progression or prior to the start of new anti-cancer treatment, whichever is sooner). These samples will be analyzed to evaluate the utility of the biopsy in distinguishing pseudoprogression (caused by tumor-infiltrating ICs) from true progression. In addition, tumor tissue biomarkers related to resistance, disease progression, and clinical benefit of atezolizumab may be analyzed.

Patients who are withdrawn from study treatment will be evaluated within 30 days and approximately 120 days after last study treatment for a treatment discontinuation visit and safety visit, respectively. Thereafter, patients will enter a post-trial access program (as applicable).

An external iDMC will evaluate safety and efficacy data according to policies and procedures detailed in an iDMC Charter (see Section 3.2).

A schedule of activities is provided in [Appendix 1](#).

### **3.2 INDEPENDENT DATA MONITORING COMMITTEE**

An iDMC will be convened to evaluate efficacy and safety data during the study. Members of the iDMC will be external to the Sponsor and will follow a charter that outlines their roles and responsibilities. The iDMC will conduct its first review of safety data when 10 patients in the safety run-in have completed at least 1 cycle of study treatment.

On the basis of the different mechanisms of action for each product, the overlapping toxicities of enzalutamide and atezolizumab are thought to not significantly increase the incidence and type of adverse events seen in respective monotherapy studies. In a study investigating enzalutamide in combination with an anti-PD-1 antibody, immune *mediated* toxicities observed were consistent with other studies investigating the anti-PD-1 antibody alone in solid tumors (Graff et al 2016).

The iDMC will specifically evaluate clinically relevant toxicities that are known to be associated with atezolizumab and/or enzalutamide. Refer to [Table 3](#) of the protocol and Section 6 of the Atezolizumab Investigator's Brochure, and enzalutamide local prescribing information. These adverse events include, but are not limited to, the following:

- Gastrointestinal toxicities including diarrhea and immune-*mediated* colitis
- Immune-*mediated* hepatitis
- Immune-*mediated* pancreatitis
- Immune-*mediated* pneumonitis
- Immune-*mediated* endocrinopathies (i.e., diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, and hypophysitis)
- Immune-*mediated* myocarditis
- Neurologic disorders including immune-*mediated* meningoencephalitis, immune-*mediated* neuropathies (i.e., myasthenic syndrome and/or myasthenia gravis, Guillain-Barré syndrome), vertigo and/or dizziness, falls, seizures and posterior reversible encephalopathy syndrome (PRES)

The iDMC will evaluate safety data and compare the type and frequency of events observed to the type and frequency of events described in the Atezolizumab Investigator's Brochure and enzalutamide local prescribing information. On the basis of this evaluation, the iDMC may recommend that an additional 10 patients be enrolled into the safety run-in portion of the study. Furthermore, the iDMC may request an extension of the observation period until the last patient has completed two cycles (42 days) or an increase in the periodic safety monitoring frequency during the randomized phase of the study.

After the safety run-in is completed, the iDMC will make a recommendation regarding initiating enrollment in the randomized phase of the study.

During the randomized phase of the study, the iDMC will continue to evaluate safety data on a periodic basis, approximately every 3 months for the first year and approximately every 6 months thereafter, until the time of the analysis of the primary efficacy endpoint. The safety data will include demographics and baseline characteristics, study drug exposure, deaths, adverse events, serious adverse events, and relevant laboratory data. Following their data review, the iDMC will provide a

recommendation as to whether the study may continue, modifications to the protocol should be implemented, or the study should be stopped.

For management of patients who experience specific adverse events during the safety run-in and randomized phase of the study, see Section 5.1.4.

One OS interim efficacy analysis will be conducted according to the methods described in Section 6.8.1. The iDMC will review results of the interim efficacy analysis and, on the basis of the predefined stopping criteria specified in the iDMC Charter, the iDMC will provide its recommendation whether to release the study results early because of substantial evidence of efficacy.

The Sponsor will remain blinded to the study results until the time of the primary analysis of the primary endpoint (or the time of the OS interim analysis if the interim results are released). All summaries and analyses by treatment arm for the iDMC review will be prepared by an external independent Data Coordinating Center (iDCC).

The final decision on whether to follow the iDMC's recommendations will rest with the Sponsor.

Any outcomes of these efficacy and safety reviews that affect study conduct will be communicated by the Sponsor in a timely manner to Health Authorities and to investigators for notification to their Institutional Review Boards/Ethics Committees (IRB/EC).

### **3.3 END OF STUDY AND LENGTH OF STUDY**

The Sponsor has decided to close Study CO39385 (IMbassador250) following the recommendation of the iDMC to terminate the trial due to futility.

### **3.4 RATIONALE FOR STUDY DESIGN**

#### **3.4.1 Rationale for Atezolizumab Dose and Schedule**

The fixed dose of 1200 mg (equivalent to an average body weight-based dose of 15 mg/kg) every three weeks (Q3W) was selected on the basis of both nonclinical studies and available clinical data from a Phase I study, PCD4989g, as described below.

The target exposure for atezolizumab was projected on the basis of clinical and nonclinical parameters, including nonclinical tissue distribution data in tumor-bearing mice, target-receptor occupancy in the tumor, and observed atezolizumab interim pharmacokinetics in humans. The target trough concentration ( $C_{\text{trough}}$ ) was projected to be 6  $\mu\text{g/mL}$  on the basis of several assumptions, including the following:

1) 95% tumor-receptor saturation is needed for efficacy and 2) the tumor interstitial concentration-to-plasma ratio is 0.30 on the basis of tissue distribution data in tumor-bearing mice.

The atezolizumab dose is also informed by available clinical activity, safety, PK, and immunogenicity data. Anti-tumor activity has been observed in doses ranging from 1 to 20 mg/kg. The maximum tolerated dose of atezolizumab was not reached, and no dose-limiting toxicities have been observed at any dose in Study PCD4989g. Available preliminary PK data (0.03–20 mg/kg) from Study PCD4989g suggest that for doses  $\geq 1$  mg/kg, overall, atezolizumab exhibits pharmacokinetics that are both linear and consistent with typical IgG1 antibodies.

ATAs to atezolizumab were associated with changes in pharmacokinetics for some patients in the lower dose cohorts (0.3, 1, and 3 mg/kg), but patients treated at 10, 15, and 20 mg/kg maintained the expected target trough levels of drug despite the detection of ATAs. To date, no relationship has been observed between the development of measurable ATAs and safety or efficacy. After review of available PK and ATA data for a range of doses, 15 mg/kg Q3W was identified as the lowest atezolizumab dosing regimen that would maintain  $C_{\text{trough}}$  at  $\geq 6$   $\mu\text{g/mL}$  while further safeguarding against interpatient variability and the potential for ATAs to lead to subtherapeutic levels of atezolizumab.

Simulations (Bai et al. 2012) do not suggest any clinically meaningful differences in exposure following a fixed dose compared with a body weight–adjusted dose. Therefore, patients in this study will be treated Q3W at a fixed dose of 1200 mg (equivalent to an average body weight–based dose of 15 mg/kg).

### **3.4.2 Rationale for Patient Population**

Despite multiple approvals in prostate cancer in the last 5 years, a strong unmet need exists for agents with durable disease control in patients who have failed an androgen synthesis inhibitor and have failed, are ineligible for, or refused a taxane regimen. Generally, outcomes in patients who have failed two prior lines of therapy remain poor with response rates of approximately 10%–15%, PFS of approximately 3 months and an OS of less than one year (Caffo et al. 2015; Roviello et al. 2015).

Docetaxel, with or without prednisone, is considered standard of care for patients with symptomatic metastatic disease (Petrylak et al. 2004; Tannock et al. 2004); however, it is poorly tolerated in the elderly. Indeed, population-based studies from Sweden and the United Kingdom suggest that only approximately 20% of patients who die from prostate cancer had received docetaxel, with significantly higher treatment rates among younger patients and patients with little comorbidities (Harris et al. 2011; Lissbrant et al. 2013). U.S. studies describe docetaxel treatment rates of approximately 40%, and 16% in the elderly (Onukwugha et al. 2011; Lafeuille et al. 2013). Low treatment rates with a taxane regimen could be attributed to different reasons such as the associated toxicity profile or unwillingness of patients to receive chemotherapy.

Recently, trials have evaluated the addition of therapies earlier in the clinical course of prostate cancer. The addition of docetaxel to ADT in patients with newly diagnosed,

metastatic HSPC was evaluated in two studies, both of which demonstrated statistically significant improvements in OS (Sweeney et al. 2015; James et al. 2016), rendering docetaxel plus ADT as a standard-of-care treatment for patients with metastatic HSPC (Parker et al. 2015; Mohler et al. 2016).

Similarly, the addition of abiraterone and prednisone/prednisolone to ADT in patients with HSPC recently demonstrated a significantly improved OS and rPFS in these patients compared to ADT alone (Fizazi et al. 2017; James et al. 2017). The LATITUDE study, which enrolled patients with HSPC, demonstrated that the concomitant administration of abiraterone with ADT would have a similar improvement in progression free survival (33 months) as sequential administration of ADT for HSPC (14.8 months) followed by abiraterone on progression to mCRPC (16.5 months) (Ryan et al. 2013; Fizazi et al. 2017), suggesting that the patients progressing after these therapies may be biologically similar.

Despite the introduction of these life-prolonging therapies for HSPC, patients who progress to develop mCRPC continue to have only limited treatment options that improve their overall outcome.

In summary, based on the poor survival prognosis despite treatment, low rates of taxane use in clinical practice and potential cross-resistance between hormonal treatments, patients who progress on an androgen synthesis inhibitor and have failed, are not fit, or unwilling, to receive subsequent taxane therapy represent a patient population in clinical practice with an unmet need. With a relatively poor survival prognosis of approximately one year, this population is considered appropriate for this Phase III study.

### **3.4.3 Rationale for Choice of Enzalutamide**

Enzalutamide is an oral androgen receptor blocker that impacts receptor signaling at multiple steps, including competitive binding to the androgen receptor, inhibition of nuclear translocation, and consequently prevention of binding of the androgen receptor to relevant activation sequences in the nucleus. Enzalutamide demonstrated statistically significant improvement over placebo in the primary endpoint of OS in the post-docetaxel setting in mCRPC patients (18.4 vs. 13.6 months; HR=0.631,  $p < 0.0001$ ). Additionally, key secondary endpoints demonstrated statistically significant differences including rPFS, time to first skeletal-related event, and time to PSA progression (Scher et al. 2012). In a second pivotal study in the pre-docetaxel setting in asymptomatic and mildly symptomatic patients, enzalutamide demonstrated statistically significant improvement over placebo in the co-primary endpoints of rPFS (not yet reached vs. 3.9 months; HR=0.186,  $p < 0.0001$ ) and OS (32.4 vs. 30.2 months; HR=0.706,  $p < 0.0001$  [Beer et al. 2014]). Other key secondary endpoints that supported the rPFS and OS data included time to first skeletal-related event, time to initiation of cytotoxic chemotherapy, and time to PSA progression.

On the basis of the results of these studies, enzalutamide has been approved for treatment of mCRPC by the U.S. Food and Drug Administration (FDA) and for treatment of adult men with mCRPC whose disease has progressed on or after docetaxel and treatment of adult men with mCRPC who are asymptomatic or mildly symptomatic after failure of ADT in whom chemotherapy is not yet clinically indicated by the European Medicines Agency (Xtandi® U.S. Prescribing Information and Summary of Product Characteristics). According to a recent study analyzing the treatment evolution for mCRPC in the United States, 75% of patients received newer hormonal treatment in first-line. Hormonal treatment remained the therapy of choice in second-line with approximately 60% of patients receiving abiraterone or enzalutamide (Flaig et al. 2015).

This study enrolls patients with mCRPC after failure of an androgen synthesis inhibitor and failure of, ineligibility for, or refusal of a taxane regimen. Enzalutamide is indicated for and is commonly used as a treatment for mCRPC and can thus be considered a reasonable standard of care and relevant control.

#### **3.4.4 Rationale for Open-Label Design**

This is an open-label study. The use of a placebo control was not considered appropriate in this elderly study population due to the patient burden associated with repeated placebo intravenous infusions and the associated risk for infusion-related complications.

#### **3.4.5 Rationale for Stratification Factors**

The randomization will be stratified on the basis of prior taxane-containing regimen for mCRPC (yes vs. no), pain severity (BPI-SF Question 3 Score  $<4$  vs.  $\geq 4$ ), presence of liver metastasis (yes vs. no), and serum LDH ( $\leq$ ULN vs  $>$ ULN).

These stratification factors have been identified as critical prognostic factors for patients with mCRPC. The magnitude of benefit in patients treated with a hormonally-based therapy may be attenuated after a taxane-containing therapy (de Bono et al. 2011; Scher et al. 2012; Ryan et al. 2013; Beer et al. 2014), possibly partly due to a cross-resistance mechanism in which microtubule inhibition may alter translocation of the androgen receptor (van Soest et al. 2013). Prior taxane treatment for mCRPC is defined as administration of at least 2 cycles of a taxane-containing regimen.

Presence of pain, visceral disease, especially liver metastases, and elevation of LDH have been consistently and independently associated with worse prognosis in multivariate analysis and disease nomograms (Armstrong et al. 2010; Halabi et al. 2014; Chi et al. 2016). Patients with a BPI-SF score on Question 3 of  $\geq 4$ , presence of lung and/or liver metastasis, and LDH elevation at baseline had inferior median OS compared to patients with respective good prognostic characteristics in the pivotal Phase III study investigating enzalutamide versus placebo post-docetaxel (Scher et al. 2012).



### **3.4.6 Rationale for Safety Run-In**

Currently, no safety data is available with the combination of atezolizumab and enzalutamide. Based on the different mechanism of action for each product, the overlapping risks of enzalutamide and atezolizumab are thought to be minimal and are not expected to significantly increase the incidence of adverse events seen in monotherapy studies. Nonetheless, potential overlapping toxicities between enzalutamide and atezolizumab might include common adverse reactions of asthenia/fatigue, back pain, decreased appetite, constipation, arthralgia, diarrhea, peripheral edema, dyspnea, musculoskeletal pain, weight decreased, headache, hypertension, and liver function abnormalities. Signs and symptoms suggestive of posterior reversible encephalopathy syndrome for enzalutamide or meningitis/encephalitis for atezolizumab have been reported.

In studies investigating the combination of atezolizumab with other anti-cancer agents, the incidence of adverse events in the treatment arms with combined use was consistent with the known safety profiles of the individual study drugs. Fatigue, decreased appetite, nausea and cough were adverse events reported in more than 10% of patients treated with atezolizumab monotherapy and in combination therapy. Through appropriate routine evaluations, investigational work-up, and early mitigations such as implementation of management guidelines, the majority of patients were able to continue atezolizumab therapy (see Atezolizumab Investigator's Brochure for detailed safety results).

In a study investigating enzalutamide in combination with an anti-PD-1 antibody in 10 patients with mCRPC, immune toxicities observed were consistent with other studies investigating the anti-PD-1 antibody alone in solid tumors (Graff et al. 2016).

Appropriate measures will be taken to ensure the safety of patients participating in this study (see Section 5.1). A safety run-in phase is incorporated into the study design, which will allow evaluation of the preliminary safety profile of atezolizumab in combination with enzalutamide prior to initiating the randomized phase of the study.

Ten patients will be enrolled and will receive atezolizumab in combination with enzalutamide. After 10 patients have received study treatment and completed at least one cycle of study treatment (21 days), an iDMC will review available data and make a recommendation regarding initiation of the randomized phase of the study.

In the randomized phase of the study, the iDMC will be convened to evaluate safety data approximately every 3 months for the first year and approximately every 6 months thereafter, until the time of the analysis of the primary efficacy endpoint. For further details regarding the iDMC see Section 3.2.

### **3.4.7 Rationale for the Use of Response Criteria**

#### **3.4.7.1 PCWG3 Criteria**

Measurable disease occurs infrequently in prostate cancer, whereas bone metastases develop in upwards to 90% of patients (Pezaro et al. 2013). An international expert committee of prostate cancer investigators, the PCWG3, met between 2012 and 2015 to formulate criteria to define meaningful clinical endpoints in mCRPC (Scher et al. 2016). This study will follow the expert recommendations to assess radiographic disease progression (see [Appendix 2](#)).

### **3.4.8 Rationale for Treatment beyond Radiographic Progression**

In studies of immunotherapeutic agents, complete response (CR), PR, and stable disease have each been shown to occur after radiographic evidence of an apparent increase in tumor burden. This initial increase in tumor burden caused by immune cell infiltration in the setting of a T-cell response has been termed pseudoprogression (Hales et al. 2010). In Study PCD4989g, evidence of tumor growth followed by a response was observed in several tumor types. In some responding patients with radiographic evidence of ICs there are no viable cancer cells.

In addition, it is likely that a patient with mCRPC has heterogeneous disease with multiple clones and foci of malignancy (clinical and/or subclinical). A patient with confirmed disease progression at one or more lesions may have other clones and foci of disease that may be benefiting from continued treatment with study medication. As a consequence, Phase III studies in mCRPC, including a study investigating enzalutamide versus placebo in the post-docetaxel setting, allowed patients to continue to receive study treatment in the absence of unequivocal clinical progression (De Bono et al. 2011; Scher et al. 2012; Ryan et al. 2013).

In this study, selected patients may be considered for treatment after PCWG3 criteria for confirmed radiographic disease progression are met, provided the benefit-risk ratio is judged to be favorable (see criteria in Section [3.1](#)) and the patient provides written consent to continue treatment. Patients should be discontinued for unacceptable toxicity or symptomatic deterioration attributed to disease progression as determined by the investigator after an integrated assessment of radiographic and biochemical data, biopsy results (if available), and clinical status.

### **3.4.9 Rationale for Biomarker Assessments**

#### **3.4.9.1 Rationale for Collection of Tumor Specimens (Fresh and/or Archival)**

Published results suggest that the expression of PD-L1 in tumors correlates with response to anti-PD-1 and anti-PD-L1 therapy (Topalian et al. 2012; Herbst et al. 2014; Borghaei et al. 2015; Fehrenbacher et al. 2016; Herbst et al. 2016; Rosenberg et al. 2016). In the current study, archival or baseline tumor specimens will be collected from patients and tested for PD-L1 expression by a central laboratory. In addition to the assessment of PD-L1 status, other exploratory biomarkers, such as

potential predictive and prognostic biomarkers related to the clinical benefit and safety of atezolizumab, tumor immunobiology, mechanisms of resistance, or tumor type will be analyzed. An archival specimen, if available, should also be submitted in patients who choose to undergo a fresh biopsy.

Patients who have additional pre-study tumor tissue samples (i.e., beyond those required to meet eligibility requirements) from procedures performed at different times during the course of their prostate cancer may consent (but are not required) to also submit these samples for central testing. Tissue samples that are obtained at multiple times from individual patients may contribute to an improved understanding of the dynamics of immunobiology and relationship with intervening anti-cancer therapy. Discussion of optional samples collected from consenting patients for exploratory biomarker analyses may be found in Section 4.5.9, Optional Samples for the Research Biosample Repository (RBR).

#### **3.4.9.2 Rationale for Collection of Tumor Specimens at Progression**

It is recommended that patients undergo tumor biopsy sample collection, if deemed clinically feasible by the investigator, at the time of first evidence of confirmed radiographic disease progression according to PCWG3 criteria. These samples will be analyzed to evaluate the utility of the biopsy in distinguishing pseudoprogression (caused by immune cell infiltration) from true progression. In addition, tumor tissue biomarkers related to resistance, disease progression, and clinical benefit of atezolizumab may be analyzed.

#### **3.4.9.3 Rationale for Blood and Urine Sampling for Biomarkers**

Blood and urine samples will be collected at baseline and during the study to evaluate changes in surrogate biomarkers. Changes in biomarkers such as cytokines associated with T-cell activation, circulating tumor DNA (ctDNA) concentration, and lymphocyte subpopulations may provide evidence of biologic activity of atezolizumab in humans. Correlations between these biomarkers and safety and efficacy endpoints will be explored to identify blood and urine-based biomarkers that might predict which patients are more likely to benefit from atezolizumab.

#### **3.4.9.4 Rationale for Sampling for Genomics Analysis**

Tumor tissue and blood samples collected at baseline and, if deemed clinically feasible by the investigator, tumor tissue collected at the time of disease progression will enable whole exome sequencing (WES) and/or next-generation sequencing (NGS) to identify somatic mutations that are predictive of response to study treatment, are associated with progression to a more severe disease state, are associated with acquired resistance to study treatment, are associated with susceptibility to developing adverse events, or can increase the knowledge and understanding of disease biology.

Genomics is increasingly informing researcher understanding of disease pathobiology. WES provides a comprehensive characterization of the exome and, along with clinical

data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

### **3.4.10 Rationale for Patient-Reported Outcome Assessments**

Note: Patient-reported outcome (PRO) assessments are no longer required.

Symptomatic bone metastases are associated with high pain severity, which interferes with patients' ability to function. These two concepts cannot be observed and therefore are best documented through standardized PROs.

In this study, PROs will provide relevant information regarding the treatment effect on prostate cancer-related symptoms and their impact on patients' daily lives. In addition, PROs will also document whether treatment efficacy comes at the expense of patients' quality of life due to deleterious treatment-related symptoms.

Patients will be reporting on very specific symptoms (e.g., pain, fatigue) and their functional impact, which are concepts proximal to patients' experience with the disease and treatment. Although an assessor bias cannot be disregarded in an open-label setting, it is unlikely that this bias would be of such magnitude as to invalidate the data collected through PROs.

Instruments implemented in the study—namely the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire (EORTC QLQ-C30), 10-point pain severity (measured at its worst) numerical rating scale (NRS) selected items from the BPI, the BPI-SF, and the Urinary Scale of the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire Prostate Module (EORTC QLQ-PR-25)—have been selected on the basis of their content validity and performance and to minimize patients' completion burden. These instruments have been previously used in clinical studies in patients with prostate cancer (Logothetis et al. 2012; Fizazi et al. 2014) and have been recommended by PCWG3 (Scher et al. 2016).

The NCI-developed PRO-CTCAE will be used to document the patients' perspective regarding commonly experienced treatment-related symptoms.

In addition, the EQ-5D-5L will be completed to inform pharmacoeconomic models.

## **4. MATERIALS AND METHODS**

### **4.1 PATIENTS**

Approximately 730 patients with mCRPC who have failed an androgen synthesis inhibitor (e.g., abiraterone) and have failed, are ineligible for, or refused a taxane regimen will be enrolled in this study.

#### 4.1.1 **Inclusion Criteria**

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age  $\geq$  18 years
- Ability to comply with the study protocol, in the investigator's judgment
- ECOG performance status of 0 or 1
- Life expectancy  $\geq$  3 months
- Histologically confirmed adenocarcinoma of the prostate
  - Disease must be either metastatic or locally confined inoperable disease that cannot be treated with definitive intent (no chance for a curative intervention)
  - Patients presenting with treatment emergent neuroendocrine differentiation, but not primary small cell features, are eligible
- Known castrate-resistant disease, defined as meeting all of the following criteria:
  - Castrate serum testosterone level  $\leq$  50 ng/dL (1.7 nmol/L) at the screening visit
  - Bilateral orchiectomy or maintenance on androgen ablation therapy with luteinizing hormone-releasing hormone agonist or antagonist or polyestradiol phosphate for the duration of the study (including the follow-up period)
- Progressive disease prior to screening by PSA or imaging per PCWG3 criteria during or following the direct prior line of therapy in the setting of medical or surgical castration. Disease progression for study entry is defined as one or more of the following three criteria:
  - PSA progression defined as two increases in PSA over a previous reference value of  $\geq$  1 ng/mL ( $\mu$ g/L) as the minimum starting value (i.e., a minimum of 3 PSA values total), with each progression measurement at least 1 week apart
  - Soft tissue disease progression defined by RECIST v1.1
    - Previously normal ( $<$  1.0 cm) lymph nodes must have grown by  $\geq$  5 mm in the short axis to be considered to have progressed
  - Bone disease progression defined by two or more new lesions on bone scan
- One prior regimen/line of a taxane-containing regimen for mCRPC or refusal or ineligibility of a taxane-containing regimen
  - Patients who have received a taxane-containing regimen for metastatic HSPC are eligible.
  - Patients who refuse or are ineligible for a taxane-containing regimen are eligible for enrollment if they have no intention to use cytotoxic chemotherapy within the next 6 months after an informed discussion.
  - A taxane-containing treatment should be considered in patients with symptomatic and extensive visceral disease who have not previously received and are good candidates for a taxane-containing regimen.

- Progression on a prior regimen/line of an androgen synthesis inhibitor for prostate cancer (e.g., abiraterone, orteronel or galeterone)
  - Patients must have received at least 28 days of an androgen synthesis inhibitor.
  - Prior treatment with first generation antiandrogens (e.g., nilutamide, bicalutamide), oral ketoconazole, vaccines (e.g., sipuleucel-T, prostrvac VF), and radium-223 dichloride is also allowed in addition to one prior regimen or line of an androgen synthesis inhibitor for prostate cancer.
- Patients receiving bisphosphonate or denosumab therapy must have been on a stable dose for at least 4 weeks.
- Availability of a representative tumor specimen from a site not previously irradiated that is suitable for determination of PD-L1 status via central testing
  - A formalin-fixed, paraffin-embedded (FFPE) tumor specimen in a paraffin block (preferred) or at least 15 slides containing unstained, freshly cut, serial sections must be submitted along with an associated pathology report prior to study enrollment. If only 10–14 slides are available, the patient may still be eligible for the study, after discussion with and approval by the Medical Monitor. If archival tumor tissue is unavailable or is determined to be unsuitable for required testing, tumor tissue must be obtained from a biopsy performed at screening. No tissue will be collected for patients enrolled in the safety run-in phase. Refer to Section 4.5.6 for additional information on tumor specimens collected at screening. Tissue from bone metastases might be acceptable after consultation with the Medical Monitor.
- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment:
  - ANC  $\geq 1.5 \times 10^9/L$  (without granulocyte colony-stimulating factor support within 2 weeks prior to Cycle 1, Day 1)
  - Lymphocyte count  $\geq 0.5 \times 10^9/L$
  - Platelet count  $\geq 100 \times 10^9/L$  without transfusion
  - Hemoglobin  $\geq 9$  g/dL

Patients may be transfused or receive erythropoietic treatment to meet this criterion

  - AST and ALT  $\leq 2.5 \times ULN$ , with the following exception:
    - Patients with documented liver metastases: AST and ALT  $\leq 5 \times ULN$
  - Serum bilirubin  $\leq 1.5 \times ULN$  with the following exception:
    - Patients with known Gilbert disease: serum bilirubin level  $\leq 3 \times ULN$
  - Creatinine clearance  $\geq 30$  mL/min (calculated using the Cockcroft-Gault formula)
  - Serum albumin  $\geq 2.5$  g/dL
  - For patients not receiving therapeutic anticoagulation: INR or aPTT  $\leq 1.5 \times ULN$  within 14 days prior to initiation of study treatment
- For patients receiving therapeutic anticoagulation: stable anticoagulant regimen

- For men who are not surgically sterile: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as defined below:

With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during the treatment period and for at least 3 months after the last dose of enzalutamide. Men must refrain from donating sperm during this same period.

With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for 3 months after the last dose of enzalutamide to avoid exposing the embryo.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

#### **4.1.2 Exclusion Criteria**

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

##### Cancer-specific exclusions

- Prior treatment with enzalutamide or any other newer hormonal androgen receptor inhibitor (e.g., apalutamide, ODM-201)
- Treatment with any approved anti-cancer therapy, including chemotherapy, immunotherapy, radiopharmaceutical or hormonal therapy (with the exception of abiraterone), within 4 weeks prior to initiation of study treatment
  - Palliative radiotherapy for bone metastases or soft tissue lesions should be completed >7 days prior to baseline imaging.
  - ADT with a gonadotropin-releasing hormone (GnRH) analog (GnRH agonist or GnRH antagonist) is allowed.
- Treatment with abiraterone within 2 weeks prior to study treatment
- Use of herbal products that may have hormonal anti-prostate cancer activity and/or are known to decrease PSA levels (e.g., saw palmetto) within 4 weeks of enrollment
- Treatment with any other investigational agent or participation in another clinical study with therapeutic intent within 4 weeks prior to initiation of study treatment
- Planned palliative procedures for alleviation of bone pain such as radiation therapy (unless completed >7 days prior to baseline imaging) and surgery.
  - Symptomatic lesions amenable to palliative radiotherapy (e.g., bone metastases or metastases causing nerve impingement) should be treated prior to initiation of study treatment.
- Structurally unstable bone lesions suggesting impending fracture

- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)
  - Patients with indwelling catheters (e.g., PleurX®) are allowed.
- Uncontrolled hypercalcemia defined as one or more of the following criteria:
  - Ionized calcium > 1.5 mmol/L
  - Serum calcium > 12 mg/dL
  - Corrected serum calcium greater than ULN (if serum albumin < 4.0 g/dL)
- Known or suspected brain metastasis or active leptomeningeal disease
- Patients with treated epidural lesions and no other epidural progression are allowed.
  - Asymptomatic metastatic lesions whose further growth would likely cause functional deficits or intractable pain (e.g., epidural metastasis that is not presently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to initiation of study treatment.

#### General medical exclusions

- Malignancies other than mCRPC within 5 years prior to initiation of study treatment
  - Patients with malignancies of a negligible risk of metastasis or death (e.g., risk of metastasis or death < 5% at 5 years) are eligible provided they meet all of the following criteria:
    - Malignancy treated with expected curative intent (e.g., adequately treated basal or squamous cell skin cancer)
    - No evidence of recurrence or metastasis by follow-up imaging and any disease-specific tumor markers
- Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction or cerebrovascular accident within 3 months prior to enrollment, unstable arrhythmia, or unstable angina
  - Patients with a known left ventricular ejection fraction (LVEF) < 40% will be excluded.
  - Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or LVEF 40%–50% must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate. Patients with a history of clinically significant cardiac disease (including anatomic abnormality, coronary artery disease, congestive heart failure, abnormal LVEF, arrhythmia, or abnormal ECG) will be required to undergo a screening echocardiogram.
  - History of clinically significant ventricular dysrhythmias (e.g., ventricular tachycardia, ventricular fibrillation, torsades de pointes)
  - History of a Mobitz II second degree or third degree heart block without permanent pacemaker in place



Hypotension (systolic blood pressure < 86 mmHg) or bradycardia with a heart rate < 50 beats per minute at the screening visit

Uncontrolled hypertension as indicated by a resting systolic blood pressure > 170 mm Hg or diastolic blood pressure > 105 mm Hg at the screening visit

- Major surgical procedure other than for diagnosis within 4 weeks prior to initiation of study treatment or anticipation of need for a major surgical procedure during the course of the study
- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications

#### Exclusion criteria related to atezolizumab

- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation
- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, or multiple sclerosis (see [Appendix 10](#) for a more comprehensive list of autoimmune diseases and immune deficiencies), with the following exceptions:

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

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

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

Rash must cover < 10% of body surface area

Disease is well controlled at baseline and requires only low-potency topical corticosteroids

No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months

- Prior allogeneic stem cell or solid organ transplantation

- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan
  - History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Positive HIV test at screening
- Active hepatitis B virus (HBV) infection (chronic or acute), defined as having a positive hepatitis B surface antigen (HBsAg) test at screening
  - Patients with a past or resolved HBV infection, defined as having a negative HBsAg test and a positive total hepatitis B core antibody (HBcAb) test at screening, are eligible for the study.
- Active hepatitis C virus (HCV) infection, defined as having a positive HCV antibody test followed by a positive HCV RNA test at screening
  - The HCV RNA test will be performed only for patients who have a positive HCV antibody test.
- Active tuberculosis
- Severe infection within 4 weeks prior to initiation of study treatment including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia
- Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment
  - Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible for the study.
- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment or anticipation of need for such a vaccine during the course of the study
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti-CTLA-4, anti-PD-1, and anti-PD-L1 therapeutic antibodies
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2) within 4 weeks or five half-lives of the drug, whichever is shorter, prior to initiation of study treatment
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [TNF]- $\alpha$  agents) within 2 weeks prior to initiation of study treatment or anticipation of need for systemic immunosuppressive medication during the course of the study, with the following exceptions:
  - Patients who received acute, low-dose, systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study.

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

The use of systemic corticosteroids of no greater than the equivalent of 10 mg of prednisone or prednisolone per day for symptomatic treatment of prostate cancer is allowed if the patient has been on a stable dose within 2 weeks prior to initiation of study treatment. There should be no plans to taper the patient off treatment or increase the dose during the study.

Patients who are tapered off systemic corticosteroids as part of a prior anti-cancer regimen must have received the last dose  $\geq 7$  days prior to initiation of study treatment.

#### Exclusion criteria related to enzalutamide

- Known allergy or hypersensitivity to components of the enzalutamide formulation
- Unable to swallow the study treatment
- Gastrointestinal disorder affecting absorption of study treatment (e.g., gastrectomy or active peptic ulcer disease within last 3 months)
- History of seizure or any condition that may predispose to seizure within 12 months prior to study treatment, including unexplained loss of consciousness or transient ischemic attack

#### Exclusion criteria unique to patients enrolled in the enzalutamide PK cohort

- Have used or plan to use the following substances within 30 days or 5 half-lives, whichever is longer, prior to initiation of study treatment through collection of the last enzalutamide PK sample:

Potent CYP2C8 and CYP3A4 inhibitors including, but not limited to, the following: boceprevir, clarithromycin, conivaptan, gemfibrozil, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole

Potent or moderate CYP3A4 and CYP2C8 inducers including, but not limited to, the following: anticonvulsants (carbamazepine, phenobarbital, phenytoin), antimycobacterials (rifabutin, rifampin, rifapentine), avasimibe, bosentan, efavirenz, etavirine, modafinil, nafcillin, St John's wort (*hypericum perforatum*)

## **4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING**

This is an open-label study.

A stratified permuted-block randomization will be implemented to balance treatment assignment across levels of stratification factors.

After written informed consent has been obtained and eligibility has been established, the study site will enter demographic and baseline characteristics in the IxRS. For those patients who are eligible for enrollment, the study site will obtain the patient's identification number and treatment assignment from the IxRS.

Patients will be randomized to one of the following treatment arms in a 1:1 ratio (experimental to control arm):

- Arm A (experimental arm): atezolizumab in combination with enzalutamide
- Arm B (control arm): enzalutamide alone

The randomization will be stratified by the following stratification factors:

- Prior taxane-containing regimen for mCRPC, defined as at least 2 cycles of a taxane-containing regimen (yes vs. no)
- Presence of liver metastasis (yes vs. no)
- Lactate dehydrogenase (LDH,  $\leq$ ULN vs  $>$ ULN)
- Pain severity (BPI-SF Question 3 score  $< 4$  vs.  $\geq 4$ )

Patient recruitment will be capped with respect to two of the stratification factors: the proportion of patients who have not received a prior taxane-containing regimen for mCRPC, and the proportion of patients with liver metastases at baseline (see Section 3.1).

### **4.3 STUDY TREATMENT**

The investigational medicinal products (IMPs) for this study are atezolizumab and enzalutamide.

#### **4.3.1 Formulation, Packaging, and Handling**

##### **4.3.1.1 Atezolizumab**

Atezolizumab will be supplied by the Sponsor as a sterile liquid in 20-mL glass vials. The vial is designed to deliver 20 mL (1200 mg) of atezolizumab solution, but may contain more than the stated volume to enable delivery of the entire 20-mL volume. For information on the formulation and handling of atezolizumab, refer to the Investigator's Brochure and Pharmacy Manual.

##### **4.3.1.2 Enzalutamide**

For information on the formulation, packaging, and handling of enzalutamide see the local prescribing information for enzalutamide.

#### **4.3.2 Dosage, Administration, and Compliance**

##### **4.3.2.1 Atezolizumab**

The dose level of atezolizumab proposed to be tested in this study is 1200 mg (equivalent to an average body weight-based dose of 15 mg/kg) administered by IV infusion Q3W (21  $\pm$  3] days).

Administration of atezolizumab will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies. For anaphylaxis precautions, see [Appendix 11](#). Atezolizumab infusions will be administered per the instructions outlined in [Table 2](#).

**Table 2 Administration of First and Subsequent Atezolizumab Infusions**

First Infusion	Subsequent Infusions
<ul style="list-style-type: none"> <li>• No premedication is permitted.</li> <li>• Vital signs (heart rate, respiratory rate, blood pressure, and temperature) should be recorded within 60 minutes prior to the infusion.</li> <li>• Atezolizumab should be infused over 60 (<math>\pm</math> 15) minutes.</li> <li>• If clinically indicated, vital signs should be recorded during the infusion at 15, 30, 45, and 60 minutes (<math>\pm</math> 5 minutes for all timepoints) during the infusion and at 30 (<math>\pm</math> 10) minutes after the infusion.</li> <li>• Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.</li> </ul>	<ul style="list-style-type: none"> <li>• If the patient experienced an infusion-related reaction with any previous infusion, premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator.</li> <li>• Vital signs should be recorded within 60 minutes prior to the infusion.</li> <li>• Atezolizumab should be infused over 30 (<math>\pm</math> 10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (<math>\pm</math> 15) minutes if the patient experienced an infusion-related reaction with the previous infusion.</li> <li>• If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be recorded during the infusion and at 30 (<math>\pm</math> 5) minutes after the infusion.</li> </ul>

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

Guidelines for medical management of infusion-related reactions (IRRs) are provided in [Table 3](#).

No dose modification for atezolizumab is allowed. Guidelines for treatment interruption or discontinuation are provided in [Section 5.1.4](#).

Any overdose or incorrect administration of study treatment should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of atezolizumab should be recorded on the Adverse Event eCRF.

#### **4.3.2.2 Enzalutamide**

Enzalutamide will be administered according to the local prescribing information. The dose of enzalutamide is 160 mg (four 40-mg capsules) administered orally once daily.

Enzalutamide doses should be taken as close to the same time each day as possible. If dosing is missed on one day for any reason, double-dosing should not occur the following day. Patients should hold their dose of enzalutamide on clinic visit days; they will be instructed when to take their study drug.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.4.

Any overdose or incorrect administration of enzalutamide should be noted on the Study Drug Administration eCRF. Adverse events associated with an overdose or incorrect administration of enzalutamide should be recorded on the Adverse Event eCRF. Section 5.3.5.12 summarizes available safety data related to overdosing of enzalutamide.

#### **4.3.3 Investigational Medicinal Product Accountability**

All IMPs required for completion of this study (atezolizumab and enzalutamide) will be provided by the Sponsor. The study site will acknowledge receipt of IMPs, using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

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

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

#### **4.3.4 Post-Study Access to Atezolizumab**

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

A patient will be eligible to receive Sponsor study drug after completing the study if all of the following conditions are met:

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

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

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

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

[http://www.roche.com/policy\\_continued\\_access\\_to\\_investigational\\_medicines.pdf](http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf)

#### **4.4 CONCOMITANT THERAPY**

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

##### **4.4.1 Permitted Therapy**

Patients who have not undergone bilateral orchiectomy must be maintained on a GnRH analog or GnRH antagonist throughout the study (i.e., both treatment phase and follow-up).

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

- Prophylactic or therapeutic anticoagulation therapy (such as low molecular weight heparin; for potential drug-drug interaction of enzalutamide and warfarin see [Appendix 13](#))
- Inactivated influenza vaccinations
- Mineralocorticoids (e.g., fludrocortisone)
- Corticosteroids administered for COPD or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency
- Standard-of-care corticosteroid use of no greater than the equivalent of 10 mg of prednisone or prednisolone per day
- Palliative surgical procedures to treat skeletal related events

- Focal palliative radiotherapy (e.g., external-beam radiotherapy to address single sites of disease). Treatment with atezolizumab and enzalutamide may be continued during palliative radiotherapy.

Patients receiving bisphosphonates or denosumab prior to enrollment should be maintained on bisphosphonate or denosumab therapy during screening and while actively treated with study drug. Initiation of bisphosphonates or denosumab is discouraged during the treatment phase of the study due to potential immunomodulatory properties. However, initiation of such treatment should not result in discontinuation of study treatment.

An analgesic log will be completed between clinic visits to document opiate analgesic use for cancer-related pain until the end of treatment visit.

Blood transfusions are allowed throughout the study.

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

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H<sub>2</sub>-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and  $\beta_2$ -adrenergic agonists; see [Appendix 11](#)).

#### **4.4.2 Cautionary Therapy for Atezolizumab**

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

Systemic corticosteroids are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (refer to [Table 3](#) of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for details).

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally



unknown. However, herbal therapies not intended for the treatment of cancer (see Section 4.4.4) may be used during the study at the discretion of the investigator.

#### **4.4.3 Cautionary Therapy for Enzalutamide**

In vitro data suggest that enzalutamide is metabolized by and/or induces CYP2C8, CYP2C9, CYP2C19, CYP3A4, uridine 5'-diphospho-glucuronosyltransferase (UGT), and the efflux transporter P-glycoprotein (P-gp) via activation of the nuclear pregnane X receptor (PXR), and there is a moderate to high potential for drug-drug interaction with any medication that is metabolized by or strongly inhibits or induces these enzymes or transporter. Co-administration of enzalutamide with substrates of these enzymes or transporter may reduce the oral bioavailability and/or increase the clearance of the substrate, resulting in decreased exposures. In consideration of the half-life of enzalutamide (approximately 1 week), effects on enzymes and transporters may persist for one month or longer after stopping enzalutamide.

[Appendix 13](#) provides a list of medicinal products that have a potential for drug-drug interactions with enzalutamide. Medications listed in [Appendix 13](#) should be avoided. When the use of one of these medications is necessary, a discussion with the Medical Monitor is encouraged. If the patient has been enrolled in the enzalutamide PK cohort, notify the Medical Monitor immediately.

If concomitant use of strong CYP2C8 inhibitors cannot be avoided, then the dose of study drug should be reduced to 80 mg/day (2 capsules).

For further information on drug-drug interactions with enzalutamide, consult the local prescribing information.

#### **4.4.4 Prohibited Therapy**

Use of the following concomitant therapies is prohibited as described below:

- Concomitant therapy intended for the treatment of cancer whether health authority-approved or experimental, is prohibited for various time periods prior to starting study treatment, depending on the agent (see Section 4.1.2), and during study treatment until disease progression is documented and the patient has discontinued study treatment, except as outlined in Section 4.4.1.

Therapy intended for the treatment of cancer may include, but is not limited to, chemotherapy, hormonal therapy (other than protocol required treatment with GnRH analog or GnRH antagonist), immunotherapy, radiotherapy including radium-223 dichloride, and herbal therapy

- Investigational therapy (other than protocol-mandated study treatment) is prohibited within 4 weeks prior to initiation of study treatment and during study treatment.
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab, and for 5 months after the last dose of atezolizumab.

- Systemic immunostimulatory agents (including, but not limited to, interferons and IL-2) are prohibited within 4 weeks or five half-lives of the drug, whichever is longer, prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.
- Systemic immunosuppressive medications (including, but not limited to, cyclophosphamide, azathioprine, methotrexate, and thalidomide) are prohibited during study treatment because these agents could potentially alter the efficacy and safety of atezolizumab.

## **4.5 STUDY ASSESSMENTS**

The schedule of activities to be performed during the study is provided in [Appendix 1](#). All activities must be performed and documented for each patient. Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

### **4.5.1 Informed Consent Forms and Screening Log**

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

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Patients who show apparent radiographic progression at a tumor response evaluation must sign a consent form at that time to acknowledge deferring other treatment options in favor of continuing study treatment.

### **4.5.2 Medical History, Concomitant Medication, and Demographic Data**

Medical history, including clinically significant diseases, surgeries, cancer history (including stage, date of diagnosis, and prior cancer therapies and procedures), and smoking history, will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to initiation of study treatment will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

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

#### **4.5.3 Physical Examinations**

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

Limited, symptom-directed physical examinations should be performed at specified post-baseline visits and as clinically indicated. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

#### **4.5.4 Vital Signs**

Vital signs will include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, and temperature.

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

#### **4.5.5 Tumor and Response Evaluations**

Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to initiation of study treatment may be used rather than repeating tests.

Tumor assessments will be performed at baseline, every 9 weeks (approximately every three cycles) following randomization for 27 weeks, and every 12 weeks thereafter regardless of dose delays, with additional scans as clinically indicated. Assessments will continue until confirmed radiographic disease progression per PCWG3 criteria (see [Appendix 2](#)).

Tumor assessments should continue regardless of whether patients start new anti-cancer therapy in the absence of confirmed radiographic disease progression unless they withdraw consent. Patients who discontinue study treatment for reasons other than confirmed radiographic disease progression (e.g., toxicity) should continue to undergo scheduled tumor assessments as if they were on the protocol schedule until the patient dies, experiences confirmed radiographic disease progression per PCWG3 criteria, withdraws consent, or until the study closes, whichever occurs first. For patients who continue to receive study treatment following confirmed radiographic disease progression, assessments will continue until loss of clinical benefit. If an optional biopsy is to be performed at approximately the same timepoint of a tumor assessment or as a result of the radiographic determination (e.g., response or progression), samples should be acquired after all imaging scans have been performed, if at all possible.

Screening assessments must include CT scans (with oral or IV contrast) or MRI scans of the chest, abdomen, and pelvis. A spiral CT scan of the chest may be obtained but is not a requirement. If a CT scan with contrast is contraindicated (i.e., in patients with contrast allergy or impaired renal clearance), a non-contrast CT scan of the chest may be performed and MRI scans of the abdomen and pelvis should be performed. A CT or MRI scan of the head should be performed as clinically indicated to confirm or refute the diagnosis of CNS metastases at baseline. CT scans of the neck or extremities should also be performed if clinically indicated and repeated throughout the study if there is evidence of disease at screening. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used.

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

A technetium-99m bone scan will be performed at screening and at each tumor assessment during the study to evaluate bone metastasis. For adequate assessment of bone lesions, it is expected that the radiologist will adjust window leveling accordingly.

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

Response and/or progression will be assessed by the investigator using PCWG3 criteria (see [Appendix 2](#)). Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits. Results must be reviewed by the investigator before dosing at the next cycle.

All primary imaging data used for tumor assessments may be collected by the Sponsor to enable the possibility of a centralized, independent review of response endpoints by an IRF.

#### **4.5.6 Laboratory, Biomarker, and Other Biological Samples**

Note: Local laboratory assessments should continue to be conducted to enable ongoing patient care, and central laboratory assessments are no longer required (as per [Appendix 1](#)).

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

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)

- Chemistry panel (serum): sodium, potassium, magnesium, chloride, bicarbonate, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, alkaline phosphatase, ALT, AST, LDH (In countries where serum bicarbonate is not considered a standard chemistry measurement [e.g., Japan], serum bicarbonate is not required as a laboratory study in the screening or on-study serum measurements.)
- Coagulation: INR and aPTT or PTT
- Thyroid function testing: thyroid-stimulating hormone, free triiodothyronine (T3, or total T3 for sites where free T3 is not performed), free thyroxine (also known as T4),
- HIV serology
- HBV serology: HBsAg, hepatitis B surface antibody, total HBcAb
  - If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test should be performed at screening.
- HCV serology: if HCV antibody test is positive, HCV RNA
  - If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has active HCV infection.
- Urinalysis (pH, specific gravity, glucose, protein, ketones, and blood); dipstick permitted
- Testosterone
- PSA

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

- Serum samples for analysis of autoantibodies: anti-nuclear antibody, anti-double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody
- Serum samples for assay of atezolizumab concentrations through use of a validated immunoassay
- Plasma samples for assay of enzalutamide and N-desmethyl enzalutamide concentrations through use of a validated methods
- Serum samples for assessment of ATAs to atezolizumab through use of validated immunoassays
- Blood, plasma, serum, and urine samples for exploratory research on biomarkers

- Archival tumor tissue sample collected at baseline for determination of tumor PD-L1 status and for exploratory research on biomarkers

A representative FFPE tumor specimen in a paraffin block (preferred) or at least 15 slides containing unstained, freshly cut, serial sections must be submitted along with an associated pathology report prior to study enrollment. If only 10–14 slides are available, the patient may still be eligible for the study, after discussion with and approval by the Medical Monitor. No tissue will be collected for patients enrolled in the safety run-in phase. After signing of the Informed Consent Form, retrieval and submission of an archival tumor sample can occur more than 28 days prior to start of study treatment but must be submitted prior to enrollment.

If archival tissue is unavailable or is determined to be unsuitable for required testing, a pretreatment tumor biopsy is required. A pretreatment tumor biopsy may also be performed if a patient's archival tissue test results do not meet eligibility criteria.

Tumor tissue should be of good quality based on total and viable tumor content. Samples should contain a minimum of 50 viable tumor cells that preserve cellular context and tissue architecture regardless of needle gauge or retrieval method. Acceptable samples include those from resections, core-needle biopsies (at least three cores, embedded in a single paraffin block), or excisional, incisional, punch, or forceps biopsies. Fine-needle aspiration (defined as samples that do not preserve tissue architecture and yield cell suspension and/or smears), brushing, cell pellets from pleural effusion, and lavage samples are not acceptable.

Tissue from soft tissue metastases or the primary tumor is preferred, with a preference for the most recent tumor tissue obtained prior to screening. Tissue from bone metastases might be acceptable after consultation with the Medical Monitor.

Patients having additional tissue samples from procedures performed at different times (e.g., earlier metastatic biopsy, prostatectomy specimen, transrectal biopsy, etc.) during the course of their prostate cancer will be requested (but not required) to also submit these samples for central testing. Tissue samples obtained at multiple times for individual patients will greatly contribute to an improved understanding of the dynamics of PD-L1 expression and relationship with intervening anti-cancer therapy.

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

- Tumor tissue sample collected at the time of progression, if deemed clinically feasible by the investigator, for exploratory research on biomarkers

Biopsies should be performed within 40 days after progression or prior to the next anti-cancer therapy, whichever is sooner. Preferably, growing lesions should be selected. Preferred samples include those from resections, core-needle biopsies (at least three cores preferred), or excisional or punch biopsies.

Tissue from soft tissue metastases or the primary tumor is preferred. Tissue from bone metastases might be acceptable after consultation with the Medical Monitor.

Exploratory biomarker research may include, but will not be limited to, analysis of PD-L1 and CD8 expression on tumor tissues, expression of T-effector-associated genes (e.g., CD8A, perforin, granzyme A, granzyme B, interferon-gamma, CXCL9, CXCL10), activated stroma-associated genes (e.g., TGF beta, fibroblast-activated protein, podoplanin, collagens, biglycan, etc.), myeloid-derived suppressor cell-associated genes (e.g., CD68, CD163, FoxP3, androgen-regulated gene 1, etc.), androgen-receptor (AR) genes, germline and somatic mutations from tumor tissue and/or from circulating tumor DNA in blood (including, but not limited to, mutation load, MSI, and MMR defects), identified through whole genome sequencing (WGS) and/or next-generation sequencing (NGS), and plasma-derived cytokines and tumor antigens.

NGS may be performed by Foundation Medicine. If performed by Foundation Medicine, the investigator can obtain results from these analyses performed on the tissue sample collected at progression in the form of an NGS report, which is available upon request directly from Foundation Medicine, given that enough tumor tissue is provided for analysis. If allowed by local laws, the investigator may share and discuss the results with the patient, unless the patient chooses otherwise. The Foundation Medicine NGS assay has not been cleared or approved by health authorities. The NGS report is generated for research purposes and is not provided for the purpose of guiding future treatment decisions. Results may not be available if the tissue does not meet testing criteria. Results will not be made available for screening tissue.

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

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.9.1), biological samples will be destroyed when the final Clinical Study Report (CSR) has been completed, with the following exceptions:

- Residual PK and ATA samples may be needed for additional immunogenicity characterization and PK and immunogenicity assay development and validation; therefore, these samples will be destroyed no later than 5 years after the final CSR has been completed.

- Blood samples collected for WGS will be stored until they are no longer needed or until they are exhausted. However, the storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).
- Blood, plasma, serum, urine, and tumor tissue samples collected for exploratory research on biomarkers will be destroyed no later than 5 years after the final CSR has been completed.

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

Data arising from sample analysis will be subject to the confidentiality standards described in Section 8.4.

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

#### **4.5.7 Electrocardiograms**

An ECG is required at screening, at Day 1 of Cycle 4 and every 4 cycles thereafter during treatment, at the end of treatment visit, and when clinically indicated. ECGs for each patient should be obtained from the same machine wherever possible. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes.

ECGs will be reviewed by the investigator to determine patient eligibility at screening. Baseline evaluation of left ventricular ejection fraction should be considered for all patients, especially in those with cardiac risk factors and/or history of coronary artery disease. Patients with a history of clinically significant cardiac disease (including anatomic abnormality, coronary disease, congestive heart failure, abnormal LVEF, arrhythmia, or abnormal ECG) will be required to undergo a screening echocardiogram.

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



#### **4.5.8 Patient-Reported Outcomes**

Note: PRO assessments are no longer required.

To more fully characterize the clinical profile of atezolizumab, PRO data will be obtained through use of the following instruments: the EORTC QLQ-C30 and selected items from the QLQ-PR25, the BPI, the BPI-SF, the PRO-CTCAE, and EQ-5D-5L. To reduce completion burden, only relevant items and scales were selected for completion.

- Question 3 from the BPI-SF (pain severity over the past 24 hours) will be completed at screening to be used for stratification.
- An analgesic log that captures the use of opioids for cancer pain only will be completed at home starting at Day 1 of Cycle 1 until the end of treatment visit (included).
- Questions 12 and 23 from the BPI (pain severity and pain interference over the past 7 days), the EORTC QLQ-C30, the 8-item Urinary Symptoms Scale (URI) from the QLQ-PR25, the EQ-5D-5L and selected items from the PRO-CTCAE will be completed at the clinical site on Day 1 of Cycle 1 and every cycle thereafter until the end of treatment visit (included) and at unscheduled visits.
- Selected scales from the EORTC QLQ-C30 (physical functioning [PF], role functioning [RF], global health status [GHS]), Question 12 from the BPI (pain severity over the past 7 days), and the complete EQ-5D-5L will also be completed by patients after end of treatment as part of the safety visit and long-term follow-up.

It is imperative that each questionnaire aforementioned be completed on Day 1 of Cycle 1. All PRO questionnaires that are completed at the clinic are required to be completed prior to the administration of study treatment and/or prior to any other study assessment(s) that could bias patient's responses.

The questionnaires will be translated in the country language(s) and as feasible in the local language.

Question 3 from the BPI-SF at screening will be administered on paper and documented on the appropriate eCRF. Patients will use an electronic device to capture all other PRO data. For situations that preclude the use of the electronic device, a backup paper option may be utilized. Instructions to use the e-device and to complete the PRO questionnaires will be provided by site staff once the patient is randomized and before initiation of study treatment. The data will be transmitted to a centralized database maintained by the vendor and will be available for access by appropriate study personnel at the site.

PRO data will not be collected for patients enrolled in the safety run-in phase of the study.

#### **4.5.8.1 EORTC QLQ-C30**

The EORTC QLQ-C30 is a validated, reliable self-reported measure (Aaronson et al. 1993; see [Appendix 4](#)). It consists of 30 questions that assess five aspects of patient functioning (physical, emotional, role, cognitive, and social), three symptom scales (fatigue, nausea and vomiting, pain), global health/QoL, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) with a recall period of the previous week. Items besides items forming the GHS scale are rated on a 4-point categorical scale. A high score (4) for a functional scale represents a high or healthy level of functioning, a high score (7) for the GHS/QoL represents a high QoL, but a high score for a symptom scale or item represents a high level of symptomatology or problems.

The EORTC QLQ-C30 will be completed in its entirety. It takes approximately 10 minutes to complete. To understand patients' symptom experience post treatment and the course of their HRQoL, the PF, RF, and GHS scales will be completed as part of the follow-up visits. These scales were selected for their content validity in documenting patients' functioning in daily activities and QoL.

#### **4.5.8.2 EORTC Quality-of-Life: Urinary Scale (QLQ-PR25)**

The 8-item urinary symptoms scale of the QLQ-PR25 form the URI scale to capture commonly reported urinary symptoms associated with prostate cancer. The items use the same rating scale as the EORTC QLQ-C30. The scale has demonstrated good psychometric performance (van Andel et al. 2008) (see [Appendix 5](#)).

The other scales from the QLQ-PR25, namely, use of incontinence aid, bowel symptoms, hormonal treatment-related symptoms, sexual activity, and sexual functioning were disregarded on the basis of their lack of content validity in patients with CRPC in second and third line of therapy.

#### **4.5.8.3 Pain Assessments: Selected Questions from BPI and BPI-SF**

The BPI and its shorter version, the BPI-SF, have become the most widely used measurement tools for assessing clinical cancer pain. The instruments allow patients to rate the severity of their pain and the degree to which their pain interferes with common dimensions of feeling and function. Both instruments include additional questions regarding analgesic use or location of pain that are not considered in the scoring algorithm for pain severity or pain interference and therefore do not contribute to the scores validity (Cleeland et al. 2009). The two instruments differ in their recall periods; the BPI uses a 7-day recall whereas the BPI-SF uses a 24-hour recall. Each item uses a 0 to 10-point NRS, with 10 indicating a high symptom severity or a high impact on functioning.

The measure of pain intensity that is most commonly used in clinical studies is a single item that asks patients to self-report their worst pain (Cleeland et al. 2013; Basch et al. 2014). Therefore, questions 3 and 12 from the BPI-SF and the BPI,

respectively, were selected as they both assess patients' pain at its worst using a 10-point NRS. Question 3 from the BPI-SF will be completed at screening for the purpose of stratifying patients on the basis of their pain severity. Question 12 and Question 23 from the BPI will allow capture of patients' symptomatic experience on a longer time window (7 days) (see [Appendix 7](#)).

#### **4.5.8.4 Analgesic Log**

A country-specific analgesic log will be used to document opiate analgesic use for cancer-related pain (e.g., name of molecule, form, dose per day).

The opiate medications prescribed for cancer-related pain will be entered into the analgesic log, and patients or caregivers will document actual opioid intake on the analgesic log. Actual intake will be transcribed into the eCRF. Oral morphine equivalents (OME) per molecule will be derived and interpreted using the Analgesic Quantification Algorithm (AQA) by the Sponsor. AQA scores range from 0 to 7, in which 0 is no analgesic use and 7 is strong opioid use (Chung et al. 2014). Equianalgesic potency conversions and AQA are displayed in [Appendix 8](#).

#### **4.5.8.5 PRO-CTCAE**

The PRO-CTCAE is an instrument developed by the National Cancer Institute in recognition that clinician reporting of symptomatic adverse events lacks reliability; clinicians under-report the incidence and severity of symptoms compared to patients' direct reports, and patient reports better reflect underlying health status than clinician reports (Basch et al. 2014). Items from the PRO-CTCAE item bank were selected on the basis of the understanding of the symptoms most commonly reported in patients who received atezolizumab in completed and ongoing clinical studies and enzalutamide as described in its local prescription information. The Sponsor therefore intends to document fatigue (2 items), GI symptoms including constipation (1 item), diarrhea (1 item), lack of appetite (2 items), and rash (1 item). In addition, a global item asking whether patients were disturbed by their side effects will be added (see [Appendix 9](#)).

#### **4.5.8.6 EQ-5D-5L**

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

## **4.5.9 Optional Samples for Research Biosample Repository**

### **4.5.9.1 Overview of the Research Biosample Repository**

Note: The collection of specimens for the RBR is no longer required.

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

Specimens for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

### **4.5.9.2 Approval by the Institutional Review Board or Ethics Committee**

Collection and submission of biological samples to the RBR is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB or EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section [4.5.9.2](#)) will not be applicable at that site.

### **4.5.9.3 Sample Collection**

The following samples will be stored in the RBR and used for research purposes, including but not limited to research on biomarkers related to atezolizumab, enzalutamide and disease biology:

- An optional blood sample collected at any time during the study
- Tumor tissue samples from biopsies performed at the investigator's discretion during the study
- Leftover blood, plasma, serum, urine and tumor tissue samples (with the exception of leftover tissue from archival FFPE blocks, which will be returned to sites) and any derivatives thereof (e.g., DNA, RNA, proteins, peptides), including leftover tissue samples from additional tumor biopsies or medically indicated procedures (e.g., bronchoscopy, esophagogastroduodenoscopy, colonoscopy) performed at the investigator's discretion during the course of the study

The above samples may be sent to one or more laboratories for analysis of germline mutations or somatic mutations via WGS, NGS, or other genomic analysis methods.

Genomics is increasingly informing researcher understanding of disease pathobiology. WGS provides a comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

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

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

#### **4.5.9.4 Confidentiality**

Specimens and associated data will be labeled with a unique patient identification number.

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

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

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

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

#### **4.5.9.5 Consent to Participate in the Research Biosample Repository**

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any

time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR specimens. Patients who decline to participate will not provide a separate signature.

The investigator should document whether the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent eCRF.

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

#### **4.5.9.6 Withdrawal from the Research Biosample Repository**

Patients who give consent to provide RBR specimens have the right to withdraw their specimens from the RBR at any time for any reason. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and, if the study is ongoing, must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the study is closed. A patient's withdrawal from Study CO39385 does not, by itself, constitute withdrawal of specimens from the RBR. Likewise, a patient's withdrawal from the RBR does not constitute withdrawal from Study CO39385.

#### **4.5.9.7 Monitoring and Oversight**

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

### **4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION**

#### **4.6.1 Study Treatment Discontinuation**

Patients must permanently discontinue study treatment (atezolizumab and/or enzalutamide) if they experience any of the following:

- Intolerable toxicity related to study treatment, including development of an immune-mediated adverse event determined by the investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event
- Any medical condition that may jeopardize the patient's safety if he or she continues study treatment

- Use of another non-protocol-specified anti-cancer therapy
- Symptomatic deterioration attributed to disease progression
- Radiographic disease progression per PCWG3 criteria, with the following exception:

Patients will be permitted to continue study treatment after experiencing confirmed radiographic disease progression per PCWG3 criteria if they meet all of the following criteria:

Evidence of clinical benefit, as determined by the investigator after an integrated assessment of radiographic data, biopsy results (if available), and clinical status

Absence of symptoms and signs (including laboratory values, such as new or worsening hypercalcemia) indicating unequivocal progression of disease

Absence of decline in ECOG performance status that can be attributed to disease progression

Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions

- Investigator or Sponsor determines it is in the best interest of the patient

Patients with rising PSA levels only (i.e., in the absence of confirmed radiographic or clinical progression) should continue to receive study treatment per PCWG3 criteria and recommendations (Scher et al. 2016). PSA rise without evidence of confirmed radiographic progression or a symptomatic skeletal-related event is strongly discouraged as a criterion to start a new systemic anti-neoplastic therapy during the first 12 weeks of therapy and is discouraged as a criterion to start a new systemic anti-neoplastic therapy throughout the study.

Focal palliative radiography (e.g., external-beam radiotherapy to address single sites of disease), initiation of bisphosphonates or denosumab, standard-of-care corticosteroid use of no greater than the equivalent of 10 mg of prednisone or prednisolone per day, and pain management are allowed and should not result in discontinuation of study treatment. However, patients should be evaluated for clinically apparent SSE.

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patient withdrawal of consent may be a reason for discontinuation of study treatment. Patients enrolled in the safety run-in period who discontinue study treatment without completing the first 21-day treatment cycle may be replaced. All other patients who discontinue study treatment prematurely will not be replaced.

Patients will return to the clinic for a treatment discontinuation visit  $\leq 30$  days after the last dose of study treatment. The visit at which the tumor assessment shows confirmed progressive disease may be used as the treatment discontinuation visit.

After treatment discontinuation, patients will be asked to return to the clinic 120 days  $\pm$  30 days after the last study treatment for a safety visit. Thereafter, patients will enter a post-trial access program.

#### **4.6.2 Patient Discontinuation from Study**

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Withdrawal of consent
- Study termination or site closure
- Patients who are, in the opinion of the Investigator or Medical Monitor, grossly non-compliant with the protocol's requirements

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. Patients enrolled in the safety run-in phase who withdraw from the study without completing the first 21-day assessment window may be replaced. All other patients who withdraw from the study prematurely will not be replaced.

#### **4.6.3 Study Discontinuation**

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

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

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

#### **4.6.4 Site Discontinuation**

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

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



## **5. ASSESSMENT OF SAFETY**

### **5.1 SAFETY PLAN**

The safety plan for patients in this study is based on clinical experience with atezolizumab and enzalutamide in completed and ongoing studies. The anticipated important safety risks are outlined below (see Sections 5.1.1 and 5.1.2). Guidelines for management of patients who experience specific adverse events are provided in Table 3 (see Section 5.1.4).

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Administration of atezolizumab will be performed in a monitored setting in which there is immediate access to trained personnel, and adequate equipment and medicine to manage potentially serious reactions. Adverse events will be reported as described in Section 5.3.5.

#### **5.1.1 Risks Associated with Atezolizumab**

Atezolizumab has been associated with risks such as the following: IRRs and immune-mediated hepatitis, pneumonitis, colitis, myocarditis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, meningoencephalitis, nephritis, and immune-mediated myositis. *Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis and macrophage activation syndrome (considered to be potential risks for atezolizumab).* Refer to Table 3 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

#### **5.1.2 Risks Associated with Enzalutamide**

Enzalutamide has been associated with risks such as the following: seizures, falls, non-pathologic fractures, cognitive disorder, PRES, neutropenia and hypertension. For further adverse reactions, warnings, and precautions for enzalutamide, see local prescribing information.

#### **5.1.3 Risks Associated with Combination Use of Atezolizumab and Enzalutamide**

On the basis of the different mechanism of action for each product, the overlapping risks of enzalutamide and atezolizumab are thought to be minimal and are not expected to significantly increase the incidence of adverse events seen in monotherapy studies. Nonetheless, potential overlapping toxicities between enzalutamide and atezolizumab might include common adverse reactions of asthenia/fatigue, back pain, decreased appetite, constipation, arthralgia, diarrhea, peripheral edema, dyspnea, musculoskeletal pain, weight decreased, headache, hypertension, and liver function abnormalities. Signs and symptoms suggestive of posterior reversible encephalopathy syndrome for

enzalutamide or meningitis encephalitis for atezolizumab have been reported. Many signs and symptoms are commonly seen in prostate cancer patients.

#### **5.1.4            Management of Patients Who Experience Specific Adverse Events**

##### **5.1.4.1        Dose Modifications**

There will be no dose modifications for atezolizumab in this study.

Study treatment may be temporarily suspended in patients experiencing toxicity considered to be related to enzalutamide. Re-starting enzalutamide at a reduced dose may be acceptable and requires written approval of the Medical Monitor (or designee).

##### **5.1.4.2        Treatment Interruption**

Atezolizumab and/or enzalutamide may be managed independently according to their respective risk profile. They may be temporarily suspended in patients experiencing toxicity considered to be related to the respective study drug. Risks associated with atezolizumab and enzalutamide are described in Section 5.1.1 and Section 5.1.2, respectively.

If corticosteroids are initiated for treatment of the toxicity, they must be tapered over  $\geq 1$  month to  $\leq 10$  mg/day oral prednisone or equivalent before atezolizumab can be resumed.

Atezolizumab and/or enzalutamide treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of an immune-*mediated* toxicity, they must be tapered over  $\geq 1$  month to  $\leq 10$  mg/day oral prednisone or equivalent before atezolizumab can be resumed. If atezolizumab and/or enzalutamide are withheld for  $> 12$  weeks, the patient will be discontinued from atezolizumab and/or enzalutamide. However, atezolizumab may be withheld for  $> 12$  weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for  $> 12$  weeks if the Medical Monitor agrees that the patient is likely to derive clinical benefit. Atezolizumab and/or enzalutamide treatment may be suspended for reasons other than toxicity (e.g., surgical procedures) with Medical Monitor approval. The investigator and the Medical Monitor will determine the acceptable length of treatment interruption.

##### **5.1.4.3        Management Guidelines**

Atezolizumab and/or enzalutamide may be managed independently according to their respective risk profile and be temporarily suspended in patients experiencing toxicity considered to be related to the respective study drug. Risks associated with atezolizumab and enzalutamide are described in Section 5.1.1 and Section 5.1.2, respectively.

Guidelines for management of patients who experience specific adverse events are provided in [Table 3](#). For adverse events associated with enzalutamide that are not listed in [Table 3](#), refer to the local prescribing information.

### ***Infusion-Related Reactions and Cytokine-Release Syndrome***

*No premedication is indicated for the administration of Cycle 1 of atezolizumab. However, patients who experience an infusion-related reaction (IRR) or cytokine-release syndrome (CRS) with atezolizumab may receive premedication with antihistamines, anti-pyretics, and/or analgesics (e.g., acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.*

*IRRs are known to occur with the administration of monoclonal antibodies and have been reported with atezolizumab. These reactions, which are thought to be due to release of cytokines and/or other chemical mediators, occur within 24 hours of atezolizumab administration and are generally mild to moderate in severity.*

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

*There may be significant overlap in signs and symptoms of IRRs and CRS, and in recognition of the challenges in clinically distinguishing between the two, consolidated guidelines for medical management of IRRs and CRS are provided in [Table 3](#).*

### ***Hemophagocytic Lymphohistiocytosis And Macrophage Activation Syndrome***

*Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS), which are considered to be potential risks for atezolizumab. For management guidelines see [Table 3](#).*

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

- *Fever  $\geq 38.5^{\circ}\text{C}$*
- *Splenomegaly*

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

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

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

**Table 3 Guidelines for Management of Patients Who Experience Specific Adverse Events**

Event	Action to Be Taken
Anaphylaxis	<ul style="list-style-type: none"> <li>• For anaphylaxis precautions, see <a href="#">Appendix 11</a>.</li> <li>• Continue enzalutamide after symptoms have resolved to baseline.</li> </ul>
<i>Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome</i>	
<p><u>Grade 1</u><sup>a</sup></p> <p><i>Fever</i><sup>b</sup> with or without constitutional symptoms</p>	<ul style="list-style-type: none"> <li>• <i>Immediately interrupt infusion.</i></li> <li>• <i>Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset.</i></li> <li>• <i>If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate.</i></li> <li>• <i>If symptoms recur, discontinue infusion of this dose.</i></li> <li>• <i>Administer symptomatic treatment,<sup>c</sup> including maintenance of IV fluids for hydration.</i></li> <li>• <i>In case of rapid decline or prolonged CRS (&gt;2 days) or in patients with significant symptoms and/or comorbidities, consider managing as per Grade 2.</i></li> <li>• <i>For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS.</i></li> <li>• <i>Continue enzalutamide after symptoms have resolved to baseline.</i></li> </ul>

ASTCT = American Society for Transplantation and Cellular Therapy; BiPAP = bi-level positive airway pressure; CAR = chimeric antigen receptor; CPAP = continuous positive airway pressure; CRS = cytokine-release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; eCRF = electronic Case Report Form; HLH = hemophagocytic lymphohistiocytosis; ICU = intensive care unit; IRR = infusion-related reaction; MAS = macrophage activation syndrome; NCCN = National Cancer Comprehensive Network; NCI = National Cancer Institute.

Note: The management guidelines have been adapted from NCCN guidelines for management of CAR T-cell-mediated toxicities (Version 2.2019).

<sup>a</sup> Grading system for management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE v4.0 should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.

<sup>b</sup> Fever is defined as temperature  $\geq 38^\circ\text{C}$  not attributable to any other cause. In patients who develop CRS and then receive anti-pyretic, anti-cytokine, or corticosteroid therapy, fever is no longer required when subsequently determining event severity (grade). In this case, the grade is driven by the presence of hypotension and/or hypoxia.

<sup>c</sup> Symptomatic treatment may include oral or IV antihistamines, anti-pyretics, analgesics, bronchodilators, and/or oxygen. For bronchospasm, urticaria, or dyspnea, additional treatment may be administered as per institutional practice.

**Table 3: Guidelines for Management of Patients Who Experience Specific AEs (cont)**

Event	Action to Be Taken
<i>Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome (cont.)</i>	
<p><b>Grade 2<sup>a</sup></b>  Fever<sup>b</sup> with hypotension not requiring vasopressors  <b>and/or</b>  Hypoxia requiring low-flow oxygen<sup>d</sup> by nasal cannula or blow-by</p>	<ul style="list-style-type: none"> <li>• Immediately interrupt infusion.</li> <li>• Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset.</li> <li>• If symptoms recur, discontinue infusion of this dose.</li> <li>• Administer symptomatic treatment.<sup>c</sup></li> <li>• For hypotension, administer IV fluid bolus as needed.</li> <li>• Monitor cardiopulmonary and other organ function closely (in the ICU, if appropriate). Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice.</li> <li>• Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in Section 5.1.4.3 and this table.</li> <li>• Consider IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours).</li> <li>• Consider anti-cytokine therapy.<sup>e</sup></li> <li>• Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize patient (monitoring in the ICU is recommended), permanently discontinue atezolizumab, and contact Medical Monitor.</li> <li>• If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab may be administered. For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for IRRs and/or CRS.</li> <li>• If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact Medical Monitor.</li> <li>• Continue enzalutamide after symptoms have resolved to baseline.</li> </ul>

ASTCT = American Society for Transplantation and Cellular Therapy; CRS = cytokine-release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; eCRF = electronic Case Report Form; HLH = hemophagocytic lymphohistiocytosis; ICU = intensive care unit; IRR = infusion-related reaction; MAS = macrophage activation syndrome; NCCN = National Cancer Comprehensive Network; NCI = National Cancer Institute.

Note: The management guidelines have been adapted from NCCN guidelines for management of chimeric antigen receptor T-cell-mediated toxicities (Version 2.2019).

<sup>a</sup> Grading system for management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE v4.0 should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.

<sup>b</sup> Fever is defined as temperature  $\geq 38$  °C not attributable to any other cause. In patients who develop CRS and then receive anti-pyretic, anti-cytokine, or corticosteroid therapy, fever is no longer required when subsequently determining event severity (grade). In this case, the grade is driven by the presence of hypotension and/or hypoxia.

<sup>c</sup> Symptomatic treatment may include oral or IV antihistamines, anti-pyretics, analgesics, bronchodilators, and/or oxygen. For bronchospasm, urticaria, or dyspnea, additional treatment may be administered as per institutional practice.

<sup>d</sup> Low flow is defined as oxygen delivered at  $\leq 6$  L/min, and high flow is defined as oxygen delivered at  $> 6$  L/min.

<sup>e</sup> There are case reports where anti-cytokine therapy has been used for treatment of CRS with immune checkpoint inhibitors (Rotz et al. 2017; Adashek and Feldman 2019), but data are limited, and the role of such treatment in the setting of antibody-associated CRS has not been established.

**Table 3 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)**

Event	Action to Be Taken
<i>Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome (cont.)</i>	
<p><b>Grade 3<sup>a</sup></b>  <i>Fever<sup>b</sup> with hypotension requiring a vasopressor (with or without vasopressin) and/or Hypoxia requiring high-flow oxygen<sup>d</sup> by nasal cannula, face mask, non-rebreather mask, or Venturi mask</i></p>	<ul style="list-style-type: none"> <li>• Permanently discontinue atezolizumab and contact Medical Monitor.<sup>f</sup></li> <li>• Administer symptomatic treatment.<sup>c</sup></li> <li>• For hypotension, administer IV fluid bolus and vasopressor as needed.</li> <li>• Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice.</li> <li>• Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in Section 5.1.4.3 and this table.</li> <li>• Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours).</li> <li>• Consider anti-cytokine therapy.<sup>e</sup></li> <li>• Hospitalize patient until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for patients who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator and in consultation with the Medical Monitor.</li> <li>• Continue enzalutamide after symptoms have resolved to baseline.</li> </ul>

ASTCT = American Society for Transplantation and Cellular Therapy; CRS = cytokine-release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; eCRF = electronic Case Report Form; HLH = hemophagocytic lymphohistiocytosis; ICU = intensive care unit; IRR = infusion-related reaction; MAS = macrophage activation syndrome; NCCN = National Cancer Comprehensive Network; NCI = National Cancer Institute.

Note: The management guidelines have been adapted from NCCN guidelines for management of chimeric antigen receptor T-cell–mediated toxicities (Version 2.2019).

<sup>a</sup> Grading system for management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE v4.0 should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.

<sup>b</sup> Fever is defined as temperature  $\geq 38$  °C not attributable to any other cause. In patients who develop CRS and then receive anti-pyretic, anti-cytokine, or corticosteroid therapy, fever is no longer required when subsequently determining event severity (grade). In this case, the grade is driven by the presence of hypotension and/or hypoxia.

<sup>c</sup> Symptomatic treatment may include oral or IV antihistamines, anti-pyretics, analgesics, bronchodilators, and/or oxygen. For bronchospasm, urticaria, or dyspnea, additional treatment may be administered as per institutional practice.

<sup>d</sup> Low flow is defined as oxygen delivered at  $\leq 6$  L/min, and high flow is defined as oxygen delivered at  $> 6$  L/min.

<sup>e</sup> There are case reports where anti-cytokine therapy has been used for treatment of CRS with immune checkpoint inhibitors (Rotz et al. 2017; Adashek and Feldman 2019), but data are limited, and the role of such treatment in the setting of antibody-associated CRS has not been established.

**Table 3 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)**

Event	Action to Be Taken
<i>Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome (cont.)</i>	
<p><b>Grade 4<sup>a</sup></b>  <i>Fever<sup>b</sup> with hypotension requiring multiple vasopressors (excluding vasopressin) and/or</i>  <i>Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)</i></p>	<ul style="list-style-type: none"> <li>• Permanently discontinue atezolizumab and contact Medical Monitor.<sup>f</sup></li> <li>• Administer symptomatic treatment.<sup>c</sup></li> <li>• Admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice.</li> <li>• Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in Section 5.1.4.3 and this table.</li> <li>• Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours).</li> <li>• Consider anti-cytokine therapy.<sup>e</sup> For patients who are refractory to anti-cytokine therapy, experimental treatments<sup>g</sup> may be considered at the discretion of the investigator and in consultation with the Medical Monitor.</li> <li>• Hospitalize patient until complete resolution of symptoms.</li> <li>• Continue enzalutamide after symptoms have resolved to baseline.</li> </ul>

ASTCT = American Society for Transplantation and Cellular Therapy; BiPAP = bi-level positive airway pressure; CAR = chimeric antigen receptor; CPAP = continuous positive airway pressure; CRS = cytokine-release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; eCRF = electronic Case Report Form; HLH = hemophagocytic lymphohistiocytosis; ICU = intensive care unit; IRR = infusion-related reaction; MAS = macrophage activation syndrome; NCCN = National Cancer Comprehensive Network; NCI = National Cancer Institute.

Note: The management guidelines have been adapted from NCCN guidelines for management of CAR T-cell-mediated toxicities (Version 2.2019).

<sup>a</sup> Grading system for management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE v4.0 should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.

<sup>b</sup> Fever is defined as temperature  $\geq 38$  °C not attributable to any other cause. In patients who develop CRS and then receive anti-pyretic, anti-cytokine, or corticosteroid therapy, fever is no longer required when subsequently determining event severity (grade). In this case, the grade is driven by the presence of hypotension and/or hypoxia.

<sup>c</sup> Symptomatic treatment may include oral or IV antihistamines, anti-pyretics, analgesics, bronchodilators, and/or oxygen. For bronchospasm, urticaria, or dyspnea, additional treatment may be administered as per institutional practice.

<sup>e</sup> There are case reports where anti-cytokine therapy has been used for treatment of CRS with immune checkpoint inhibitors (Rotz et al. 2017; Adashek and Feldman 2019), but data are limited, and the role of such treatment in the setting of antibody-associated CRS has not been established.

<sup>f</sup> Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor. For subsequent infusions, administer oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS. Premedication with corticosteroids and extending the infusion time may also be considered after consulting the Medical Monitor and considering the benefit–risk ratio.

<sup>g</sup> Refer to Riegler et al. (2019) for information on experimental treatments for CRS.



**Table 3 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)**

Event	Action to Be Taken
<b>Gastrointestinal toxicity</b>	
Diarrhea or colitis, Grade 1	<ul style="list-style-type: none"> <li>• Continue atezolizumab.</li> <li>• Initiate symptomatic treatment.</li> <li>• Endoscopy is recommended if symptoms persist for &gt;7 days.</li> <li>• Monitor closely.</li> <li>• Continue enzalutamide.</li> </ul>
Diarrhea or colitis, Grade 2	<ul style="list-style-type: none"> <li>• Withhold atezolizumab for up to 12 weeks after event onset.<sup>a</sup></li> <li>• Initiate symptomatic treatment.</li> <li>• Patient referral to GI specialist is recommended.</li> <li>• For recurrent events or events that persist &gt;5 days, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent.</li> <li>• If event resolves to Grade 1 or better, resume atezolizumab.<sup>b</sup></li> <li>• If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.<sup>c</sup></li> <li>• Continue enzalutamide.</li> </ul>
Diarrhea or colitis, Grade 3	<ul style="list-style-type: none"> <li>• Withhold atezolizumab for up to 12 weeks after event onset.<sup>a</sup></li> <li>• Refer patient to GI specialist for evaluation and confirmatory biopsy.</li> <li>• Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.</li> <li>• If event resolves to Grade 1 or better, resume atezolizumab.<sup>b</sup></li> <li>• If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.<sup>c</sup></li> <li>• Consider withholding enzalutamide.</li> <li>• Resume enzalutamide if event resolves to Grade ≤2 <b>and/or</b> if event is deemed unrelated to enzalutamide. In case of uncertain relationship and/or recurrent Grade 3 or 4 diarrhea or colitis, rechallenge with enzalutamide might be considered after consultation with the Medical Monitor.<sup>d</sup></li> </ul>

GI=gastrointestinal.

<sup>a</sup> Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

<sup>c</sup> Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

<sup>d</sup> Approval by the investigator and Medical Monitor must be documented.

**Table 3 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)**

Event	Action to Be Taken
Gastrointestinal toxicity (cont.)	
Diarrhea or colitis, Grade 4	<ul style="list-style-type: none"> <li>• Permanently discontinue atezolizumab and contact Medical Monitor. <sup>c</sup></li> <li>• Refer patient to gastrointestinal specialist for evaluation and confirmation biopsy.</li> <li>• Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.</li> <li>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.</li> <li>• If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.</li> <li>• Consider withholding enzalutamide.</li> <li>• Resume enzalutamide if event resolves to Grade ≤2 and/or if event is deemed unrelated to enzalutamide. In case of uncertain relationship and/or recurrent Grade 3 or 4 diarrhea or colitis, rechallenge with enzalutamide might be considered after consultation with the Medical Monitor. <sup>d</sup></li> </ul>
Hepatotoxicity	
Hepatic event, Grade 1	<ul style="list-style-type: none"> <li>• Continue atezolizumab.</li> <li>• Monitor LFTs until values resolve to within normal limits.</li> <li>• Continue enzalutamide.</li> </ul>

LFT=liver function test.

<sup>c</sup> Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-*mediated* event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

<sup>d</sup> Approval by the investigator and Medical Monitor must be documented.

**Table 3 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)**

Event	Action to Be Taken
Hepatotoxicity (cont.)	
Hepatic event, Grade 2	<p><b>All events:</b></p> <ul style="list-style-type: none"> <li>• Monitor LFTs more frequently until return to baseline values.</li> </ul> <p><b>Events of &gt; 5 days in duration:</b></p> <ul style="list-style-type: none"> <li>• Withhold atezolizumab for up to 12 weeks after event onset. <sup>a</sup></li> <li>• Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent.</li> <li>• If event resolves to Grade 1 or better resume atezolizumab. <sup>b</sup></li> <li>• If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. <sup>c</sup></li> <li>• Continue enzalutamide.</li> </ul>
Hepatic event, Grade 3 or 4	<ul style="list-style-type: none"> <li>• Permanently discontinue atezolizumab and contact Medical Monitor. <sup>c</sup></li> <li>• Consider patient referral GI specialist for evaluation and liver biopsy to establish etiology of hepatic injury.</li> <li>• Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent.</li> <li>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.</li> <li>• If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.</li> <li>• Consider withholding enzalutamide.</li> <li>• Resume enzalutamide if event resolves to Grade ≤2 <b>and/or</b> if event is deemed unrelated to enzalutamide. In case of uncertain relationship and/or recurrent Grade 3 or 4 hepatic injury, rechallenge with enzalutamide might be considered after consultation with the Medical Monitor. <sup>d</sup></li> </ul>
Pulmonary events, including pneumonitis	
Pulmonary event, Grade 1	<ul style="list-style-type: none"> <li>• Continue atezolizumab and monitor closely.</li> <li>• Re-evaluate on serial imaging.</li> <li>• Consider patient referral to pulmonary specialist.</li> <li>• Continue enzalutamide.</li> </ul>

GI=gastrointestinal; LFT=liver function test.

<sup>a</sup> Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

<sup>c</sup> Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

<sup>d</sup> Approval by the investigator and Medical Monitor must be documented.

**Table 3 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)**

Event	Action to Be Taken
Pulmonary events, including pneumonitis (cont.)	
Pulmonary event, Grade 2	<ul style="list-style-type: none"> <li>• Withhold atezolizumab for up to 12 weeks after event onset. <sup>a</sup></li> <li>• Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL.</li> <li>• Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent.</li> <li>• If event resolves to Grade 1 or better, resume atezolizumab. <sup>b</sup></li> <li>• If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. <sup>c</sup></li> <li>• For recurrent events, treat as a Grade 3 or 4 event.</li> <li>• Continue enzalutamide.</li> </ul>
Pulmonary event, Grade 3 or 4	<ul style="list-style-type: none"> <li>• Permanently discontinue atezolizumab and contact Medical Monitor. <sup>c</sup></li> <li>• Bronchoscopy or BAL is recommended.</li> <li>• Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent.</li> <li>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.</li> <li>• If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.</li> <li>• Consider withholding enzalutamide.</li> <li>• Resume enzalutamide if event resolves to Grade ≤2 and/or if event is deemed unrelated to enzalutamide. In case of uncertain relationship and/or recurrent Grade 3 or 4 pneumonitis, rechallenge with enzalutamide might be considered after consultation with the Medical Monitor. <sup>d</sup></li> </ul>
Cardiac events	
Immune-mediated myocarditis, Grade 1	<ul style="list-style-type: none"> <li>• Refer patient to cardiologist.</li> <li>• Initiate treatment as per institutional guidelines.</li> <li>• Continue enzalutamide.</li> </ul>

BAL=bronchoalveolar lavage.

<sup>a</sup> Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

<sup>c</sup> Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

<sup>d</sup> Approval by the investigator and Medical Monitor must be documented.

**Table 3 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)**

Event	Action to Be Taken
Cardiac events (cont.)	
Immune-mediated myocarditis, Grade 2	<ul style="list-style-type: none"> <li>• Withhold atezolizumab for up to 12 weeks after event onset and contact Medical Monitor. <sup>a</sup></li> <li>• Refer patient to cardiologist.</li> <li>• Initiate treatment per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, VAD as appropriate.</li> <li>• Consider treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.</li> <li>• If event resolves to Grade 1 or better, resume atezolizumab. <sup>b</sup></li> <li>• If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. <sup>c</sup></li> <li>• Continue enzalutamide.</li> </ul>
Immune-mediated myocarditis, Grade 3 or 4	<ul style="list-style-type: none"> <li>• Permanently discontinue atezolizumab and contact Medical Monitor. <sup>c</sup></li> <li>• Refer patient to cardiologist.</li> <li>• Initiate treatment per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, and VAD as appropriate.</li> <li>• Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.</li> <li>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.</li> <li>• If event resolves to Grade 1 or better, taper corticosteroids over <math>\geq 1</math> month.</li> <li>• Consider withholding enzalutamide.</li> <li>• Resume enzalutamide if event resolves to Grade <math>\leq 2</math> and/or if event is deemed unrelated to enzalutamide. In case of uncertain relationship and/or recurrent Grade 3 or 4 myocarditis, rechallenge with enzalutamide might be considered after consultation with the Medical Monitor. <sup>d</sup></li> </ul>

ECMO =extracorporeal membrane oxygenation; VAD=ventricular assist device.

<sup>a</sup> Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to  $\leq 10$  mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

<sup>b</sup> If corticosteroids have been initiated, they must be tapered over  $\geq 1$  month to  $\leq 10$  mg/day oral prednisone or equivalent before atezolizumab can be resumed.

<sup>c</sup> Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

<sup>d</sup> Approval by the investigator and Medical Monitor must be documented.

**Table 3 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)**

Event	Action to Be Taken
Endocrine events	
Asymptomatic hypothyroidism	<ul style="list-style-type: none"> <li>• Continue atezolizumab.</li> <li>• Initiate treatment with thyroid replacement hormone.</li> <li>• Monitor TSH weekly.</li> <li>• Continue enzalutamide.</li> </ul>
Symptomatic hypothyroidism	<ul style="list-style-type: none"> <li>• Withhold atezolizumab.</li> <li>• Initiate treatment with thyroid-replacement hormone.</li> <li>• Monitor TSH weekly.</li> <li>• Consider patient referral to endocrinologist.</li> <li>• Resume atezolizumab when symptoms are controlled and thyroid function is improving.</li> <li>• Consider withholding enzalutamide.</li> <li>• Resume enzalutamide when diagnosis of immune-<i>mediated</i> hypothyroidism is confirmed and appropriate treatment is initiated or symptoms are controlled and thyroid function is improving.</li> </ul>
Asymptomatic hyperthyroidism	<p><b>TSH <math>\geq</math> 0.1 mU/L and <math>&lt;</math> 0.5 mU/L:</b></p> <ul style="list-style-type: none"> <li>• Continue atezolizumab.</li> <li>• Monitor TSH every 4 weeks.</li> <li>• Continue enzalutamide.</li> </ul> <p><b>TSH <math>&lt;</math> 0.1 mU/L:</b></p> <ul style="list-style-type: none"> <li>• Follow guidelines for symptomatic hyperthyroidism.</li> </ul>
Symptomatic hyperthyroidism	<ul style="list-style-type: none"> <li>• Withhold atezolizumab.</li> <li>• Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed.</li> <li>• Consider patient referral to endocrinologist.</li> <li>• Resume atezolizumab when symptoms are controlled and thyroid function is improving.</li> <li>• Permanently discontinue atezolizumab and contact Medical Monitor for life-threatening immune-<i>mediated</i> hyperthyroidism. <sup>c</sup></li> <li>• Consider withholding enzalutamide.</li> <li>• Resume enzalutamide when symptoms are controlled and thyroid function is improving.</li> </ul>

TSH=thyroid-stimulating hormone.

<sup>c</sup> Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-*mediated* event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

**Table 3 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)**

Event	Action to Be Taken
<b>Endocrine events (cont.)</b>	
Symptomatic adrenal insufficiency, Grade 2	<ul style="list-style-type: none"> <li>• Withhold atezolizumab for up to 12 weeks after event onset. <sup>a</sup></li> <li>• Refer patient to endocrinologist.</li> <li>• Perform appropriate imaging.</li> <li>• Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.</li> <li>• If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab. <sup>b</sup></li> <li>• If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. <sup>c</sup></li> <li>• Continue enzalutamide.</li> </ul>
Symptomatic adrenal insufficiency, Grade 3 or 4	<ul style="list-style-type: none"> <li>• Withhold atezolizumab for up to 12 weeks after event onset. <sup>a</sup></li> <li>• Refer patient to endocrinologist.</li> <li>• Perform appropriate imaging.</li> <li>• Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.</li> <li>• If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab. <sup>b</sup></li> <li>• If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. <sup>c</sup></li> <li>• Consider withholding enzalutamide.</li> <li>• Resume enzalutamide if event resolves to Grade <math>\leq 2</math> and/or if event is deemed unrelated to enzalutamide. In case of uncertain relationship and/or recurrent Grade 3 or 4 symptomatic adrenal insufficiency, rechallenge with enzalutamide might be considered after consultation with the Medical Monitor. <sup>d</sup></li> </ul>

<sup>a</sup> Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to  $\leq 10$  mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

<sup>b</sup> If corticosteroids have been initiated, they must be tapered over  $\geq 1$  month to  $\leq 10$  mg/day oral prednisone or equivalent before atezolizumab can be resumed.

<sup>c</sup> Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

<sup>d</sup> Approval by the investigator and Medical Monitor must be documented.

**Table 3 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)**

Event	Action to Be Taken
Endocrine events (cont.)	
Hyperglycemia, Grade 1 or 2	<ul style="list-style-type: none"> <li>• Continue atezolizumab.</li> <li>• Initiate treatment with insulin if needed.</li> <li>• Monitor for glucose control.</li> <li>• Continue enzalutamide.</li> </ul>
Hyperglycemia, Grade 3 or 4	<ul style="list-style-type: none"> <li>• Withhold atezolizumab.</li> <li>• Initiate treatment with insulin.</li> <li>• Monitor for glucose control.</li> <li>• Resume atezolizumab when symptoms resolve and glucose levels are stable.</li> <li>• Consider withholding enzalutamide.</li> <li>• Resume enzalutamide when symptoms resolve and glucose levels are stable.</li> </ul>
Hypophysitis (pan-hypopituitarism), Grade 2	<ul style="list-style-type: none"> <li>• Withhold atezolizumab for up to 12 weeks after event onset.<sup>a</sup></li> <li>• Refer patient to endocrinologist.</li> <li>• Perform brain MRI (pituitary protocol).</li> <li>• Initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.</li> <li>• Initiate hormone replacement as clinically needed.</li> <li>• If event resolves to Grade 1 or better, resume atezolizumab.<sup>b</sup></li> <li>• If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.<sup>c</sup></li> <li>• For recurrent hypophysitis, treat as a Grade 4 event.</li> <li>• Continue enzalutamide.</li> </ul>

MRI=magnetic resonance imaging.

<sup>a</sup> Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

<sup>c</sup> Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.



**Table 3 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)**

Event	Action to Be Taken
Endocrine events (cont.)	
<ul style="list-style-type: none"> <li>• Hypophysitis (pan-hypopituitarism), Grade 3</li> </ul>	<ul style="list-style-type: none"> <li>• Withhold atezolizumab for up to 12 weeks after event onset. <sup>a</sup></li> <li>• Refer patient to endocrinologist.</li> <li>• Perform brain MRI (pituitary protocol).</li> <li>• Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.</li> <li>• Initiate hormone replacement as clinically needed.</li> <li>• If event resolves to Grade 1 or better, resume atezolizumab. <sup>b</sup></li> <li>• If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. <sup>c</sup></li> <li>• For recurrent hypophysitis, treat as a Grade 4 event.</li> <li>• Consider withholding enzalutamide.</li> <li>• Resume enzalutamide if event resolves to Grade ≤2 and/or if event is deemed unrelated to enzalutamide. In case of uncertain relationship and/or recurrent Grade 3 hypophysitis, rechallenge with enzalutamide might be considered after consultation with the Medical Monitor. <sup>d</sup></li> </ul>

MRI=magnetic resonance imaging.

- <sup>a</sup> Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.
- <sup>b</sup> If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.
- <sup>c</sup> Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.
- <sup>d</sup> Approval by the investigator and Medical Monitor must be documented.

**Table 3 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)**

Event	Action to Be Taken
Endocrine events (cont.)	
Hypophysitis (pan-hypopituitarism), Grade 4	<ul style="list-style-type: none"> <li>• Permanently discontinue atezolizumab and contact Medical Monitor. <sup>c</sup></li> <li>• Refer patient to endocrinologist.</li> <li>• Perform brain MRI (pituitary protocol).</li> <li>• Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.</li> <li>• Initiate hormone replacement as clinically needed.</li> <li>• Consider withholding enzalutamide.</li> <li>• Resume enzalutamide if event resolves to Grade <math>\leq 2</math> and/or if event is deemed unrelated to enzalutamide. In case of uncertain relationship and/or recurrent Grade 4 hypophysitis, rechallenge with enzalutamide might be considered after consultation with the Medical Monitor. <sup>d</sup></li> </ul>

MRI=magnetic resonance imaging.

<sup>c</sup> Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

<sup>d</sup> Approval by the investigator and Medical Monitor must be documented.

**Table 3 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)**

Event	Action to Be Taken
Dermatologic events	
Dermatologic event, Grade 1	<ul style="list-style-type: none"> <li>• Continue atezolizumab.</li> <li>• Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).</li> <li>• Continue enzalutamide.</li> </ul>
Dermatologic event Grade 2	<ul style="list-style-type: none"> <li>• Continue atezolizumab.</li> <li>• Consider patient referral to dermatologist.</li> <li>• Initiate treatment with topical corticosteroids.</li> <li>• Consider treatment with higher-potency topical corticosteroids if event does not improve</li> <li>• Continue enzalutamide.</li> </ul>
Dermatologic event, Grade 3	<ul style="list-style-type: none"> <li>• Withhold atezolizumab for up to 12 weeks after event onset. <sup>a</sup></li> <li>• Refer patient to dermatologist.</li> <li>• Initiate treatment with 10 mg/day oral prednisone or equivalent, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours.</li> <li>• If event resolves to Grade 1 or better, resume atezolizumab. <sup>b</sup></li> <li>• If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. <sup>c</sup></li> <li>• Consider withholding enzalutamide.</li> <li>• Resume enzalutamide if event resolves to Grade <math>\leq 2</math> and/or if event is deemed unrelated to enzalutamide. In case of uncertain relationship and/or recurrent Grade 3 dermatologic event, rechallenge with enzalutamide might be considered after consultation with the Medical Monitor. <sup>d</sup></li> </ul>

<sup>a</sup> Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to  $\leq 10$  mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

<sup>b</sup> If corticosteroids have been initiated, they must be tapered over  $\geq 1$  month to  $\leq 10$  mg/day oral prednisone or equivalent before atezolizumab can be resumed.

<sup>c</sup> Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

<sup>d</sup> Approval by the investigator and Medical Monitor must be documented.

**Table 3 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)**

Event	Action to Be Taken
Dermatologic event, Grade 4	<ul style="list-style-type: none"> <li>• Permanently discontinue atezolizumab and contact Medical Monitor.<sup>c</sup></li> <li>• Consider withholding enzalutamide.</li> <li>• Resume enzalutamide if event resolves to Grade <math>\leq 2</math> and/or if event is deemed unrelated to enzalutamide. In case of uncertain relationship and/or recurrent Grade 4 dermatologic event, rechallenge with enzalutamide might be considered after consultation with the Medical Monitor.<sup>d</sup></li> </ul>
Neurologic disorders	
Immune-mediated neuropathy, Grade 1	<ul style="list-style-type: none"> <li>• Continue atezolizumab.</li> <li>• Investigate etiology.</li> <li>• Continue enzalutamide.</li> </ul>
Immune-mediated neuropathy, Grade 2	<ul style="list-style-type: none"> <li>• Withhold atezolizumab for up to 12 weeks after event onset.<sup>a</sup></li> <li>• Investigate etiology.</li> <li>• Initiate treatment as per institutional guidelines.</li> </ul> <p>If event resolves to Grade 1 or better, resume atezolizumab.<sup>b</sup></p> <p>If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.<sup>c</sup></p> <ul style="list-style-type: none"> <li>• Continue enzalutamide.</li> </ul>
Immune-mediated neuropathy, Grade 3 or 4	<ul style="list-style-type: none"> <li>• Permanently discontinue atezolizumab and contact Medical Monitor.<sup>c</sup></li> <li>• Initiate treatment as per institutional guidelines.</li> <li>• Consider withholding enzalutamide.</li> <li>• Resume enzalutamide if event resolves to Grade <math>\leq 2</math> and/or if event is deemed unrelated to enzalutamide. In case of uncertain relationship and/or recurrent Grade 3 or 4 neuropathy, rechallenge with enzalutamide might be considered after consultation with the Medical Monitor.<sup>d</sup></li> </ul>

<sup>a</sup> Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to  $\leq 10$  mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

<sup>b</sup> If corticosteroids have been initiated, they must be tapered over  $\geq 1$  month to  $\leq 10$  mg/day oral prednisone or equivalent before atezolizumab can be resumed.

<sup>c</sup> Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

<sup>d</sup> Approval by the investigator and Medical Monitor must be documented.

**Table 3 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)**

Event	Action to Be Taken
Myasthenia gravis and Guillain-Barré syndrome (any grade)	<ul style="list-style-type: none"> <li>• Permanently discontinue atezolizumab and contact Medical Monitor. <sup>c</sup></li> <li>• Refer patient to neurologist.</li> <li>• Initiate treatment as per institutional guidelines.</li> <li>• Consider initiation of 1–2 mg/kg/day oral or IV prednisone or equivalent.</li> <li>• Consider withholding enzalutamide.</li> <li>• Resumption of enzalutamide might be considered in patients who have fully recovered and/or if event is deemed unrelated to enzalutamide after consultation with the Medical Monitor.</li> </ul>
Immune-mediated meningoencephalitis, all grades or PRES	<ul style="list-style-type: none"> <li>• Permanently discontinue atezolizumab and contact Medical Monitor. <sup>c</sup></li> <li>• Refer patient to neurologist.</li> <li>• Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.</li> <li>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.</li> <li>• If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.</li> <li>• Permanently discontinue enzalutamide.</li> </ul>
Seizure, all grades	<ul style="list-style-type: none"> <li>• Withhold atezolizumab.</li> <li>• Refer patient to neurologist.</li> <li>• Initiate treatment as per institutional guidelines.</li> <li>• Resume atezolizumab in patients who have fully recovered <b>and</b> if event is deemed unrelated to atezolizumab.</li> <li>• Permanently discontinue enzalutamide.</li> </ul>

PRES= posterior reversible encephalopathy syndrome.

<sup>c</sup> Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

**Table 3 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)**

Event	Action to Be Taken
Pancreatic events, including pancreatitis	
Amylase and/or lipase elevation, Grade 2	<ul style="list-style-type: none"> <li>• Continue atezolizumab.</li> <li>• Monitor amylase and lipase weekly.</li> <li>• For prolonged elevation (e.g., &gt;3 weeks), consider treatment with 10 mg/day oral prednisone or equivalent.</li> <li>• Continue enzalutamide.</li> </ul>
Amylase and/or lipase elevation, Grade 3 or 4	<ul style="list-style-type: none"> <li>• Withhold atezolizumab for up to 12 weeks after event onset.<sup>a</sup></li> <li>• Refer patient to GI specialist.</li> <li>• Monitor amylase and lipase every other day.</li> <li>• If no improvement, consider treatment with 1–2 mg/kg/day oral prednisone or equivalent.</li> <li>• If event resolves to Grade 1 or better, resume atezolizumab.<sup>b</sup></li> <li>• If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.<sup>c</sup></li> <li>• For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor.<sup>c</sup></li> <li>• Consider withholding enzalutamide.</li> <li>• Resume enzalutamide if event resolves to Grade ≤2 <b>and/or</b> if event is deemed unrelated to enzalutamide. In case of uncertain relationship and/or recurrent Grade 3 or 4 amylase or lipase elevation, rechallenge with enzalutamide might be considered after consultation with the Medical Monitor.<sup>d</sup></li> </ul>

GI = gastrointestinal.

- <sup>a</sup> Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.
- <sup>b</sup> If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.
- <sup>c</sup> Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.
- <sup>d</sup> Approval by the investigator and Medical Monitor must be documented.

**Table 3 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)**

Event	Action to Be Taken
Pancreatic events, including pancreatitis (cont.)	
Immune-mediated pancreatitis, Grade 2	<ul style="list-style-type: none"> <li>• Withhold atezolizumab for up to 12 weeks after event onset. <sup>a</sup></li> <li>• Refer patient to GI specialist.</li> <li>• Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.</li> <li>• If event resolves to Grade 1 or better, resume atezolizumab. <sup>b</sup></li> <li>• If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. <sup>c</sup></li> <li>• For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor. <sup>c</sup></li> <li>• Continue enzalutamide.</li> </ul>
Immune-mediated pancreatitis, Grade 3	<ul style="list-style-type: none"> <li>• Withhold atezolizumab for up to 12 weeks after event onset. <sup>a</sup></li> <li>• Refer patient to GI specialist.</li> <li>• Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.</li> <li>• If event resolves to Grade 1 or better, resume atezolizumab. <sup>b</sup></li> <li>• If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. <sup>c</sup></li> <li>• For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor. <sup>c</sup></li> <li>• Consider withholding enzalutamide.</li> <li>• Resume enzalutamide if event resolves to Grade <math>\leq 2</math> and/or if event is deemed unrelated to enzalutamide. In case of uncertain relationship and/or recurrent Grade 3 pancreatitis, rechallenge with enzalutamide might be considered after consultation with the Medical Monitor. <sup>d</sup></li> </ul>

GI = gastrointestinal.

<sup>a</sup> Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to  $\leq 10$  mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

<sup>b</sup> If corticosteroids have been initiated, they must be tapered over  $\geq 1$  month to  $\leq 10$  mg/day oral prednisone or equivalent before atezolizumab can be resumed.

<sup>c</sup> Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

<sup>d</sup> Approval by the investigator and Medical Monitor must be documented.

**Table 3 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)**

Event	Action to Be Taken
Pancreatic events, including pancreatitis (cont.)	
Immune-mediated pancreatitis, Grade 4	<ul style="list-style-type: none"> <li>• Permanently discontinue atezolizumab and contact Medical Monitor. <sup>c</sup></li> <li>• Refer patient to GI specialist.</li> <li>• Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.</li> <li>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.</li> <li>• If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.</li> <li>• Consider withholding enzalutamide.</li> <li>• Resume enzalutamide if event resolves to Grade ≤2 and/or if event is deemed unrelated to enzalutamide. In case of uncertain relationship and/or recurrent Grade 4 pancreatitis, re-challenge with enzalutamide might be considered after consultation with the Medical Monitor. <sup>d</sup></li> </ul>
Ocular events	
Ocular event, Grade 1	<ul style="list-style-type: none"> <li>• Continue atezolizumab.</li> <li>• Patient referral to ophthalmologist is strongly recommended.</li> <li>• Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy.</li> <li>• If symptoms persist, treat as a Grade 2 event.</li> <li>• Continue enzalutamide.</li> </ul>

GI = gastrointestinal.

<sup>c</sup> Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

<sup>d</sup> Approval by the investigator and Medical Monitor must be documented.



**Table 3 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)**

Event	Action to Be Taken
Ocular events	
Ocular event, Grade 2	<ul style="list-style-type: none"> <li>• Withhold atezolizumab for up to 12 weeks after event onset. <sup>a</sup></li> <li>• Patient referral to ophthalmologist is strongly recommended.</li> <li>• Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy.</li> <li>• If event resolves to Grade 1 or better, resume atezolizumab. <sup>b</sup></li> <li>• If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. <sup>c</sup></li> <li>• Continue enzalutamide</li> </ul>
Ocular event, Grade 3 or 4	<ul style="list-style-type: none"> <li>• Permanently discontinue atezolizumab and contact Medical Monitor. <sup>c</sup></li> <li>• Refer patient to ophthalmologist.</li> <li>• Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent.</li> <li>• If event resolves to Grade 1 or better, taper corticosteroids over <math>\geq 1</math> month.</li> <li>• Consider withholding enzalutamide.</li> <li>• Resume enzalutamide if event resolves to Grade <math>\leq 2</math> and/or if event is deemed unrelated to enzalutamide. In case of uncertain relationship and/or recurrent Grade 3 or 4 ocular event, rechallenge with enzalutamide might be considered after consultation with the Medical Monitor. <sup>d</sup></li> </ul>
Renal events	
Renal event, Grade 1	<ul style="list-style-type: none"> <li>• Continue atezolizumab.</li> <li>• Monitor kidney function, including creatinine, closely until values resolve to within normal limits or to baseline values.</li> <li>• Continue enzalutamide.</li> </ul>

<sup>a</sup> Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to  $\leq 10$  mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

<sup>b</sup> If corticosteroids have been initiated, they must be tapered over  $\geq 1$  month to  $\leq 10$  mg/day oral prednisone or equivalent before atezolizumab can be resumed.

<sup>c</sup> Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

<sup>d</sup> Approval by the investigator and Medical Monitor must be documented.

**Table 3 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)**

Event	Action to Be Taken
Renal events (cont.)	
Renal event, Grade 2	<ul style="list-style-type: none"> <li>• Withhold atezolizumab for up to 12 weeks after event onset. <sup>a</sup></li> <li>• Refer patient to renal specialist.</li> <li>• Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone.</li> <li>• If event resolves to Grade 1 or better, resume atezolizumab. <sup>b</sup></li> <li>• If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. <sup>c</sup></li> <li>• Continue enzalutamide.</li> </ul>
Renal event, Grade 3 or 4	<ul style="list-style-type: none"> <li>• Permanently discontinue atezolizumab and contact Medical Monitor.</li> <li>• Refer patient to renal specialist and consider renal biopsy.</li> <li>• Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone.</li> <li>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.</li> <li>• If event resolves to Grade 1 or better, taper corticosteroids over <math>\geq 1</math> month.</li> <li>• Consider withholding enzalutamide.</li> <li>• Resume enzalutamide if event resolves to Grade <math>\leq 2</math> and/or if event is deemed unrelated to enzalutamide. In case of uncertain relationship and/or recurrent Grade 3 or 4 event, rechallenge with enzalutamide might be considered after consultation with the Medical Monitor. <sup>d</sup></li> </ul>
Other Grade 3 or 4 treatment-mediated toxicities (i.e., not described above)	<ul style="list-style-type: none"> <li>• Withhold atezolizumab and/or enzalutamide if event is considered to be related to the <u>respective</u> study drug.</li> <li>• Resume atezolizumab and/or enzalutamide if event resolves to Grade <math>\leq 2</math> or baseline.</li> <li>• In case of uncertain relationship and/or recurrent Grade 3 or 4 event, consult with the Medical Monitor.</li> </ul>

<sup>a</sup> Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to  $\leq 10$  mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

<sup>b</sup> If corticosteroids have been initiated, they must be tapered over  $\geq 1$  month to  $\leq 10$  mg/day oral prednisone or equivalent before atezolizumab can be resumed.

<sup>c</sup> Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

<sup>d</sup> Approval by the investigator and Medical Monitor must be documented.

**Table 3 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)**

Event	Action to Be Taken
<i>Immune-mediated</i> myositis	
<i>Immune-mediated</i> myositis, Grade 1	<ul style="list-style-type: none"> <li>• Continue atezolizumab.</li> <li>• Refer patient to rheumatologist or neurologist.</li> <li>• Initiate treatment as per institutional guidelines.</li> </ul>
<i>Immune-mediated</i> myositis, Grade 2	<ul style="list-style-type: none"> <li>• Withhold atezolizumab for up to 12 weeks after event onset<sup>a</sup> and contact Medical Monitor.</li> <li>• Refer patient to rheumatologist or neurologist.</li> <li>• Initiate treatment as per institutional guidelines.</li> <li>• Consider treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.</li> <li>• If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.</li> <li>• If event resolves to Grade 1 or better, resume atezolizumab.<sup>b</sup></li> <li>• If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.<sup>c</sup></li> </ul>

<sup>a</sup> Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

<sup>c</sup> Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the *immune-mediated* event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

**Table 3 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)**

Event	Action to Be Taken
Immune-mediated myositis (cont.)	
Immune-mediated myositis, Grade 3	<ul style="list-style-type: none"> <li>• Withhold atezolizumab for up to 12 weeks after event onset<sup>a</sup> and contact Medical Monitor.</li> <li>• Refer patient to rheumatologist or neurologist.</li> <li>• Initiate treatment as per institutional guidelines.</li> <li>• Respiratory support may be required in more severe cases.</li> <li>• Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.</li> <li>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.</li> <li>• If event resolves to Grade 1 or better, resume atezolizumab.<sup>b</sup></li> <li>• If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.<sup>c</sup></li> <li>• For recurrent events, treat as a Grade 4 event.</li> </ul>

<sup>a</sup> Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

<sup>c</sup> Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

**Table 3 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)**

Event	Action to Be Taken
<i>Immune-mediated</i> myositis (cont.)	
<i>Immune-mediated</i> myositis, Grade 4	<ul style="list-style-type: none"> <li>• Permanently discontinue atezolizumab and contact Medical Monitor. <sup>c</sup></li> <li>• Refer patient to rheumatologist or neurologist.</li> <li>• Initiate treatment as per institutional guidelines.</li> <li>• Respiratory support may be required in more severe cases.</li> <li>• Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.</li> <li>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.</li> <li>• If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.</li> </ul>
<i>Suspected HLH or MAS</i>	<ul style="list-style-type: none"> <li>• <i>Permanently discontinue atezolizumab and contact Medical Monitor.</i></li> <li>• <i>Consider patient referral to hematologist.</i></li> <li>• <i>Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines.</i></li> <li>• <i>Consider initiation of IV corticosteroids and/or an immunosuppressive agent.</i></li> <li>• <i>If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.</i></li> <li>• <i>If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.</i></li> </ul>

*HLH =hemophagocytic lymphohistiocytosis; IV=intravenous; MAS =macrophage activation syndrome.*

<sup>a</sup> *Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.*

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

<sup>c</sup> *Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.*

## **5.2 SAFETY PARAMETERS AND DEFINITIONS**

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

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

### **5.2.1 Adverse Events**

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

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, regardless of whether it is considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.10
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study treatment
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

### **5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)**

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

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

This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.

- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)

- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study treatment
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

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

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

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

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

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

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

Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, or hyperthyroidism and hypophysitis

- Hepatitis, or AST or ALT > 10 × ULN
- Systemic lupus erythematosus
- Neurologic disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Nephritis
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine-release syndrome, influenza-like illness, *and* systemic inflammatory response syndrome
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

### **5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS**

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

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

#### **5.3.1 Adverse Event Reporting Period**

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

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

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



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

### 5.3.2 Eliciting Adverse Event Information

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

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

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

### 5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v4.0) will be used for assessing adverse event severity. Table 4 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

**Table 4 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE**

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

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

Note: On the basis of the most recent version of NCI CTCAE (v4.0), which can be found at [http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/ctc.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

<sup>a</sup> Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

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

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

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

### 5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to study treatment, indicating "yes" or "no"

accordingly. The following guidance should be taken into consideration (see also [Table 5](#)):

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

**Table 5 Causal Attribution Guidance**

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

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

### **5.3.5 Procedures for Recording Adverse Events**

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

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

#### **5.3.5.1 Infusion-Related Reactions**

Adverse events that occur during or within 24 hours after study treatment administration and are judged to be related to study treatment infusion should be captured as a diagnosis (e.g., "infusion-related reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms

should be recorded on the dedicated Infusion-Related Reaction eCRF. If a patient experiences both a local and systemic reaction to the same dose of study treatment, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF.

#### **5.3.5.2 Diagnosis versus Signs and Symptoms**

For adverse events other than infusion-related reactions (see Section 5.3.5.1), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

#### **5.3.5.3 Adverse Events That Are Secondary to Other Events**

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

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

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

#### **5.3.5.4 Persistent or Recurrent Adverse Events**

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes

more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

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

### **5.3.5.5 Abnormal Laboratory Values**

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

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

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

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

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

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

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

### **5.3.5.6 Abnormal Vital Sign Values**

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

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

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

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

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

### **5.3.5.7 Abnormal Liver Function Tests**

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

- Treatment-emergent ALT or AST  $> 3 \times$  baseline value in combination with total bilirubin  $> 2 \times$  ULN (of which  $\geq 35\%$  is direct bilirubin)
- Treatment-emergent ALT or AST  $> 3 \times$  baseline value in combination with clinical jaundice

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

### **5.3.5.8 Deaths**

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of prostate cancer should be recorded on the Death Attributed to Progressive Disease eCRF. All other on-study deaths, regardless of

relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). An independent monitoring committee will monitor the frequency of deaths from all causes.

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

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

#### **5.3.5.9 Preexisting Medical Conditions**

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

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

#### **5.3.5.10 Lack of Efficacy or Worsening of Prostate Cancer**

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on PCWG3 criteria. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

#### **5.3.5.11 Hospitalization or Prolonged Hospitalization**

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

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

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

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

The patient has not experienced an adverse event.

- Hospitalization due solely to progression of the underlying cancer

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

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

#### **5.3.5.12 Adverse Events Associated with an Overdose or Error in Drug Administration**

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study treatment should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section [5.4.2](#)).

No safety data related to overdosing of atezolizumab are available.

On the basis of the increased incidence of seizures that were observed at doses higher than 160 mg (3.5%; 3 of 85 patients), patients may be at increased risk of seizures following an overdose of enzalutamide. One overdose was reported in the clinical study database for a patient enrolled in the early phase dose-escalation Study S-3100-1-01 who was assigned a dose of 240 mg/day, but received 640 mg/day for 8 days. During this period, adverse events for Grade 2 fatigue and asthenia were reported and were self-limiting. Enzalutamide was studied in Study S-3100-1-01 of castration-resistant prostate cancer patients in daily doses ranging from 30 mg to 600 mg. Five dose-limiting toxicities were observed in four patients at doses exceeding 160 mg per day. These included three seizures (1 each at 360-, 480-, and 600-mg doses [the 600-mg case included confusion]) and rash (1 at 600 mg).

### **5.3.5.13 Patient-Reported Outcome Data**

Adverse event reports will not be derived from PRO data and safety analyses will not be performed using PRO data. No attempt will be made to reconcile the findings from reports of treatment-related symptoms by the clinicians (NCI CTCAE) and from the patients (NCI PRO-CTCAE) given the different ways in which these two data sources are collected.

Although sites are not expected to review the PRO data, it is possible that an investigator could become aware of PRO data that may be indicative of an adverse event. Under these circumstances, the investigator will determine whether the criteria for an adverse event have been met and, if so, will report the event on the Adverse Event eCRF.

## **5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR**

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

- Serious adverse events (see Section 5.4.2 for further details)
- Adverse events of special interest (see Section 5.4.2 for further details)
- Pregnancies (see Section 5.4.3 for further details)

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

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

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



#### **5.4.1 Emergency Medical Contacts**

##### **Medical Monitor Contact Information**

Medical Monitor: [REDACTED], M.D., Ph.D.

Email: [REDACTED]

Telephone No.: [REDACTED]

##### **Back-up Medical Monitor Contact Information**

Medical Monitor: [REDACTED], M.D.

Email: [REDACTED]

Telephone No.: [REDACTED]

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

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

##### **5.4.2.1 Events That Occur prior to Study Treatment Initiation**

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

##### **5.4.2.2 Events That Occur after Study Treatment Initiation**

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

In the event that the EDC system is unavailable, the Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using

the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur > 90 days after the last dose of study treatment are provided in Section 5.6.

### **5.4.3 Reporting Requirements for Pregnancies**

#### **5.4.3.1 Pregnancies in Female Partners of Male Patients**

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 3 months after the last dose of enzalutamide. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study treatment. When permitted, the pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the investigator and/or obstetrician.

## **5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS**

### **5.5.1 Investigator Follow-Up**

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

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

All pregnancies reported during the study should be followed until pregnancy outcome.

### **5.5.2 Sponsor Follow-Up**

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from

hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

## **5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD**

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

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

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

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

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference documents:

- Atezolizumab Investigator's Brochure
- Local prescribing information for enzalutamide

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

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

## **6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN**

Analysis populations are defined as follows:

- The intent-to-treat (ITT) population is defined as all randomized patients regardless of whether the assigned study treatment was received. For efficacy analyses, patients will be analyzed according to their randomized treatment assignment.
- Objective response rate in soft tissue lesions will be analyzed in patients in the ITT population with measurable soft tissue lesions at baseline.
- The duration of response (DOR)-evaluable population is defined as patients with an objective response in soft tissue lesions.
- The safety population is defined as patients who received any amount of any component of the study treatments (atezolizumab, or enzalutamide). Patients will be allocated to treatment arms according to the treatment they actually received (i.e., patients randomized to enzalutamide alone who received at least one full or partial dose of atezolizumab will be included in the atezolizumab arm for safety).

Safety run-in patients are not included in the populations defined above. Safety and efficacy data from these patients will be presented separately.

Baseline measurements are the last available data obtained prior to the patient receiving the first dose of study treatment.

### **6.1 DETERMINATION OF SAMPLE SIZE**

A total of approximately 730 patients are planned to be enrolled in the global phase of this study: 10 patients during the non-randomized safety run-in phase, and approximately 720 during the randomized phase of the study.

The sample size of 10 patients for the safety run-in is based on clinical considerations. No statistical hypothesis tests will be performed on data from the safety run-in phase.

The final analysis of the primary endpoint of OS will be performed when approximately 540 deaths have occurred in the ITT population (75% of 720 patients).

The calculations are based on the following assumptions:

- Log-rank test
- 1:1 randomization
- Two-sided alpha of 0.05
- Median OS for the control (enzalutamide alone) arm of 12 months and estimated median OS in the experimental arm of 16.7 months, corresponding to a HR of 0.72
- A drop-out rate of approximately 5% per 2-year period
- One interim OS analysis

It is projected that an observed HR of  $\leq 0.84$  will result in a statistically significant difference between treatment arms (i.e., the HR of 0.84 will be the minimally detectable difference at the final analysis). This corresponds to an improvement of median OS from 12 months to 14.3 months.

In case of proportional hazards, 540 events would provide 97% power to detect a difference in the duration of OS given the above assumptions. However, computer simulations show that the actual power of the log-rank test is likely lower in case of control patients switching to subsequent lines of immunotherapy following progression. For example, if 15% of control patients receive subsequent treatment providing similar OS benefit as atezolizumab, the reduction in power is projected to be approximately 6%.

Recruitment of the planned 720 patients is projected to be completed within 13 months. On the basis of the above assumptions, the required number of OS events for the final analysis is projected to occur at approximately Month 38 after randomizing the first patient.

## **6.2 SUMMARIES OF CONDUCT OF STUDY**

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

## **6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS**

Demographic characteristics, such as age, sex, race/ethnicity, baseline disease characteristics, etc., will be summarized by treatment arm for the ITT population. Continuous variables will be summarized using means, standard deviations, medians, and ranges. Categorical variables will be summarized by frequencies and percentages.

## **6.4 EFFICACY ANALYSES**

### **6.4.1 Primary Efficacy Endpoint**

The primary efficacy endpoint is OS, defined as the time from randomization to death from any cause. Data for patients who are not reported as having died at the date of analysis will be censored at the last date known to be alive. Data for patients who do not have post-baseline information will be censored at the date of randomization plus 1 day.

The primary comparison of OS between treatment arms will be based on a stratified log-rank test. The HR for death in the experimental arm compared with the control arm will be estimated using a stratified Cox regression model, and the 95% CI will be provided. The stratification factors will be the same as the randomization stratification factors; however, stratification factors may be combined for analysis purposes if

necessary to minimize small stratum cell sizes. Combination of stratification factors, if any, would be specified in the SAP prior to analysis. Values for the stratification factors will be as recorded in the IxRS at the time of randomization. Results from an unstratified analysis will also be presented.

Kaplan-Meier plots will be constructed to provide a visual description of the difference between the treatment and control arms. Kaplan-Meier methodology will also be used to estimate median OS for each treatment arm. Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median OS for each treatment arm.

The OS rate at key timepoints (12 months, 24 months) will be estimated using Kaplan-Meier methodology, along with 95% CIs calculated using the standard error derived from Greenwood's formula. The 95% CI for the difference in OS rates between the two treatment arms will be estimated by use of the normal approximation method.

#### **6.4.2            Secondary Efficacy Endpoints**

Analyses of the primary endpoint of OS and the key secondary efficacy endpoints listed below will be performed in a hierarchical fashion with type 1 error control (see Section 6.8.1). The primary endpoint of OS will be analyzed first. If the null hypothesis for the OS endpoint is rejected, then the key secondary endpoints will be in the order provided:

1. Time to cancer-related pain progression
2. Time to first symptomatic skeletal event (SSE)
3. rPFS

If for one endpoint in this list the null hypothesis cannot be rejected, then the results for this and all following endpoints are not considered to be statistically significant. Analyses of other secondary endpoints of this study will be considered as descriptive in nature, and no formal hypothesis testing will be conducted.

##### **6.4.2.1        Radiographic PFS and Other Time-to-Event Endpoints**

The following secondary time -to -event endpoints will be analyzed using similar methods as those described for OS above:

- Time to cancer-related pain progression
- Time to first SSE
- rPFS
- Immune-modified rPFS
- Time to initiation or increased opiate analgesic use for cancer pain
- Time to PSA progression

Data for patients who do not have post-baseline information will be censored at the date of randomization plus 1 day. Data for patients who have not experienced an event at the time of the analysis will be censored at the last available assessment.

Hazard ratios and 95% CI from a stratified Cox proportional hazards model will be provided. Kaplan-Meier methodology will be used to estimate median time to event and the 95% CI will be provided. Analyses of rPFS will also include the rPFS rate at 6 and 12 months.

#### **6.4.2.2 PSA Response Rates**

An estimate of the PSA response rate and its 95% CI will be calculated for each treatment arm using the Clopper Pearson method. The difference of PSA response rates and 95% CI between the two treatment arms will be estimated by use of the normal approximation to the binomial distribution.

#### **6.4.2.3 Objective Response Rate in Soft Tissue Lesions**

The analysis population for objective response rate (ORR) will be all patients in the ITT population with measurable soft tissue lesions at baseline.

ORR is defined as the proportion of patients who had a confirmed response in soft tissue lesions. An estimate of ORR will be calculated for each treatment arm, and its 95% CI will be calculated using the Clopper Pearson method. The CI for the difference in ORRs between the two treatment arms will be determined using the normal approximation to the binomial distribution.

#### **6.4.3 Exploratory Efficacy Endpoints**

The methodologies outlined for the ORR in soft tissue lesions analysis will be used for the DCR analysis.

The following exploratory time-to-event endpoints will be analyzed using the same methods as outlined in the section on secondary time-to-event endpoints.

- Modified PFS based on radiographic disease progression and unequivocal clinical progression
- DOR in soft tissue lesions
- Time to initiation of next systemic anti-cancer therapy
- Time to unequivocal clinical progression

DOR will be assessed in patients who had an objective response in soft tissue lesions as determined by the investigator.

DOR is defined as the time from the first occurrence of a CR or PR (whichever status is recorded first) until the first date progressive disease or death is documented, whichever occurs first. Patients who have not progressed and who have not died at the time of

analysis will be censored at the time of last tumor assessment date. If no tumor assessments were performed after the date of the first occurrence of a CR or PR, DOR will be censored at the date of the first occurrence of a CR or PR plus 1 day.

The statistical methods applied to DOR will be the same as for rPFS described above. However, it should be noted that DOR is evaluated in a non-randomized subset of patients (those who achieved an objective response in soft tissue); therefore, results of this analysis will be provided for descriptive purposes only.

#### **6.4.4            Subgroup Analyses**

Subgroup analyses will be performed in an exploratory manner in order to investigate consistency of the treatment effect across different subgroups. Subgroup categories will include demographic characteristics (e.g., age, sex, and race/ethnicity), baseline disease characteristics (e.g., prior taxane-containing therapy, type of disease progression [PSA only vs. radiographic disease progression], sites of metastases), and stratification factors, and other subgroups as appropriate.

Subgroup analyses will use similar methods as those used for the study population as a whole. Results for efficacy parameters in subgroups will be presented in Forest plots and descriptive summary tables.

It is not planned to investigate the homogeneity of the treatment effect across individual centers because with approximately 180 recruiting centers the average number of patients per center would be too small to detect any meaningful differences between them.

Additional details will be provided in the Statistical Analysis Plan (SAP) prior to performing the analyses.

#### **6.5                SAFETY ANALYSES**

Safety analyses will be performed on the safety-evaluable population, which is defined as all randomized patients from the global enrollment phase who receive any amount of any component of study treatments. Patients will be summarized according to the treatment actually received. Specifically, for patients randomized to the enzalutamide alone arm, if atezolizumab was received by mistake, patients will be grouped under the atezolizumab arm in the safety analyses.

Exposure to study treatment will be summarized to include treatment duration, number of doses, and dose intensity.

Verbatim description of adverse events will be coded to MedDRA preferred terms and graded according to NCI CTCAE v4.0. All adverse events occurring during or after the first study-drug dose will be summarized by treatment arm and NCI CTCAE grade. In addition, serious adverse events, Grade  $\geq$  3 adverse events, adverse events of special



interest (see Section 5.2.2), adverse events leading to treatment discontinuation, and/or modification will be summarized.

Laboratory abnormalities will be summarized by treatment arm and grade.

Changes in selected vital signs will be summarized by treatment arm.

Deaths and causes of death reported during the study treatment period and those reported during the follow-up period after treatment completion/discontinuation will be summarized by treatment arm.

In addition, safety data will be presented in summary tables split by subgroups defined by age, sex, and race/ethnicity, as well as other potential risk factors as appropriate. Additional details will be provided in the SAP prior to performing the analyses.

## **6.6 PHARMACOKINETIC ANALYSES**

PK analyses will be performed on the PK-evaluable population, which is defined as patients who have received at least one dose of study drug and have at least one post-dose PK sample. The PK population for each study drug and specific timepoint will vary, depending on the availability of results with adequately documented dose time and PK sampling time.

Atezolizumab serum concentration data (minimum [ $C_{min}$ ] and maximum [ $C_{max}$ ]) will be reported and summarized (e.g., mean, standard deviation, coefficient of variation [CV%], median, range, geometric mean, geometric mean coefficient of variation [CVb]) for each cycle where collected as appropriate.

Plasma concentrations of enzalutamide and N-desmethyl enzalutamide will be reported and summarized using descriptive statistics as described above for each cycle and treatment arm, as appropriate. Data may be excluded from PK analysis if a patient has taken concomitant medications that are known to affect enzalutamide PK (see [Appendix 13](#)). For patients enrolled in China, plasma samples for enzalutamide and N-desmethyl enzalutamide will not be collected.

Additional PK and pharmacodynamic analyses will be conducted as appropriate on the basis of the available data.

## **6.7 IMMUNOGENICITY ANALYSES**

The immunogenicity analyses will include all patients enrolled, with patients grouped according to treatment received.

The numbers and proportions of ATA-positive patients and ATA-negative patients at baseline (baseline prevalence) and after baseline (post-baseline incidence) will be summarized by treatment group. When determining post-baseline incidence, patients

are considered to be ATA positive if they are ATA negative or are missing data at baseline but develop an ATA response following study drug exposure (treatment-induced ATA response), or if they are ATA positive at baseline and the titer of one or more post-baseline samples is at least 0.60-titer units higher than the titer of the baseline sample (treatment-enhanced ATA response). Patients are considered to be ATA negative if they are ATA negative or are missing data at baseline and all post-baseline samples are negative, or if they are ATA positive at baseline but do not have any post-baseline samples with a titer that is at least 0.60-titer units higher than the titer of the baseline sample (treatment unaffected).

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

## **6.8 INTERIM ANALYSES**

### **6.8.1 Planned Interim Analyses**

A total of two analyses of OS will be performed: one interim analysis and the final analysis.

The interim analysis of the primary endpoint of OS will be performed when approximately 432 deaths have occurred (60% of 720 patients), corresponding to approximately 80% of the 540 deaths required for the final analysis of OS. The required number of deaths for the interim analysis is projected to occur at approximately Month 27 after randomizing the first patient.

The Lan-DeMets alpha-spending function approach will be used to determine the boundary values for statistical significance at the interim and final analysis (DeMets and Lan 1994).

For the primary endpoint of OS, the stopping boundaries will be based on the O'Brien-Fleming alpha-spending function. At both the interim and final OS analysis, key secondary endpoints listed in Section 6.4.2 will be evaluated for statistical significance only if the difference in duration of OS is statistically significant at the appropriate boundary level. For these secondary endpoints, the boundaries for statistical significance will be based on a Pocock alpha-spending function. Key secondary endpoints will be tested at the appropriate significance level in the order specified in Section 6.4.2. If for one endpoint in this list the null hypothesis cannot be rejected, then the results for this and all following endpoints are not statistically significant.

The hierarchical testing procedure with the boundaries determined as described above ensures that the overall type I error for the primary and key secondary endpoints will be controlled at 0.05 (Hung et al. 2007; Glimm et al. 2010).

The interim OS analysis will be performed by the iDCC and reviewed by the iDMC (see Section 3.2). The Sponsor will remain blinded to the results. On the basis of its review

of the data, the iDMC will provide a recommendation as to whether to release the study results early because of substantial evidence of efficacy.

### **6.8.2 Optional Interim Analysis**

To adapt to information that may emerge during the course of this study, the Sponsor may choose to conduct one interim efficacy analysis for the primary endpoint of OS beyond what is specified in Section 6.8.1. The decision to conduct the optional interim analysis, along with the rationale, timing, and statistical details for the analysis, will be documented in the SAP, and the SAP will be submitted to relevant health authorities at least 2 months prior to the conduct of the interim analysis.

If an interim analysis is conducted, the Sponsor will remain blinded. The interim analysis will be conducted by the iDCC and reviewed by the iDMC. Interactions between the iDMC and Sponsor will be carried out as specified in the iDMC Charter.

If there is a potential for the study to be stopped for positive efficacy as a result of the interim analysis, the type I error rate will be controlled using the same Lan-DeMets approach as for the planned interim analysis described above.

## **7. DATA COLLECTION AND MANAGEMENT**

### **7.1 DATA QUALITY ASSURANCE**

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

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

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

PRO data, other than the data obtained from Question 3 of the BPI-SF at screening, will be collected through the use of an electronic device provided by a vendor. For situations that preclude the use of the electronic device, a backup paper option may be utilized. The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with FDA, regulations for electronic records (21 CFR Part 11). The electronic data are available for view access only via secure access to a vendor hosted, password protected web portal. Only identified and trained users may view the

data, and their actions become part of the audit trail. The Sponsor will have view access only. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

## **7.2 ELECTRONIC CASE REPORT FORMS**

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

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

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

## **7.3 ELECTRONIC PATIENT-REPORTED OUTCOME DATA**

An electronic device will be used to capture PRO data at the site visit and at home between study visits. It is critical that patients are reminded to bring their provisioned electronic device at each visit. The data will be transmitted to a centralized database maintained by the electronic device vendor. Once the study is complete, the data, audit trail, and study and system documentation will be archived. The investigator will receive patient data for the site in both human and machine-readable formats on an archival-quality compact disc that must be kept with the study records as source data. Acknowledgement of receipt of the compact disc is required. In addition, the Sponsor will receive all data in a machine-readable format.

## **7.4 SOURCE DATA DOCUMENTATION**

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

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

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be

entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

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

## **7.5 USE OF COMPUTERIZED SYSTEMS**

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

## **7.6 RETENTION OF RECORDS**

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

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

## **8. ETHICAL CONSIDERATIONS**

### **8.1 COMPLIANCE WITH LAWS AND REGULATIONS**

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S.

Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

## **8.2 INFORMED CONSENT**

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Informed Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

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

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

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

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

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

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

### **8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE**

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

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

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

### **8.4 CONFIDENTIALITY**

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

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

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

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will

be available in accordance with the effective Roche policy on study data publication (see Section 9.5).

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

Study data, which may include data on germline mutations, may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted clinical study reports and other summary reports will be provided upon request.

## **8.5 FINANCIAL DISCLOSURE**

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., receipt of the last data point required for the final analysis of the primary efficacy endpoint or sponsor decision to end the study, whichever occurs first).

## **9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION**

### **9.1 STUDY DOCUMENTATION**

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

### **9.2 PROTOCOL DEVIATIONS**

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



### **9.3 SITE INSPECTIONS**

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

### **9.4 ADMINISTRATIVE STRUCTURE**

This study will be sponsored and managed by F. Hoffmann-La Roche Ltd. Approximately 180 sites globally will participate in the study and approximately 730 patients will be enrolled.

Enrollment in the safety run-in and randomized phases of the study will occur through an IxRS system. In the randomized phase, randomization will be managed by IxRS. Central facilities will be used for study assessments throughout the study (e.g., specified laboratory tests, PK analyses, and medical imaging).

Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

An iDMC will be convened to evaluate safety data during the study according to policies and procedures detailed in an iDMC Charter.

### **9.5 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS**

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

[http://www.roche.com/roche\\_global\\_policy\\_on\\_sharing\\_of\\_clinical\\_study\\_information.pdf](http://www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf)

The results of this study may be published or presented at scientific congresses. For all clinical studies in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical study results within 6 months after the availability of the respective CSR. In addition, for all clinical studies in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

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

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

## **9.6            PROTOCOL AMENDMENTS**

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

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

## 10. REFERENCES

- Aaronson NK, Ahmedzai, Bergman B, et al. A quality-of-life instrument for use in clinical trials in oncology. *J Natl Cancer Inst* 1993;85:365–76.
- Adashek ML, Feldman M. Cytokine release syndrome resulting from anti-programmed death-1 antibody: raising awareness among community oncologist. J Oncol Practice* 2019;15:502–4.
- Antonarakis ES, Lu C, Wang H, et al. AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer. *N Engl J Med* 2014;371:1028–38.
- Apetoh L, Ghiringhelli F, Tesniere A, et al. Toll-like receptor 4-dependent contribution of the immune system to anticancer chemotherapy and radiotherapy. *Nat Med* 2007;13:1050–9.
- Ardiani A, Farsaci B, Rogers CJ, et al. Combination therapy with a second-generation androgen receptor antagonist and a metastasis vaccine improves survival in a spontaneous prostate cancer model. *Clin Cancer Res* 2013;19:22.
- Armstrong AJ, Garrett-Mayer E, de Wit R. Prediction of survival following first-line chemotherapy in men with castration-resistant metastatic prostate cancer. *Clin Cancer Res* 2010;16:203–11.
- Arredouani MS, Tseng-Rogenski SS, Hollenbeck BK, et al. Androgen ablation augments human HLA2.1-restricted T cell responses to PSA self-antigen in transgenic mice. *Prostate* 2010;70:1002–11.
- Azad AA, Volik SV, Wyatt AW, et al. Androgen receptor gene aberrations in circulating cell-free DNA: biomarkers of therapeutic resistance in castration-resistant prostate cancer. *Clin Cancer Res* 2015;21:2315–24.
- Baade PD, Youlten DR, Krnjacki LJ. International epidemiology of prostate cancer: geographical distribution and secular trends. *Mol Nutr Food Res* 2009;53:171–84.
- Bai S, Jorga K, Xin Y, et al. A guide to rational dosing of monoclonal antibodies. *Clin Pharmacokinet* 2012;51:119–35.
- Basch E, Autio K, Ryan CJ, et al. Abiraterone acetate plus prednisone versus prednisone alone in chemotherapy-naive men with metastatic castration-resistant prostate cancer: patient-reported outcome results of a randomised Phase 3 trial. *Lancet Oncol* 2013;14:1193–9.
- Basch E, Reeve BB, Mitchell SA, et al. Development of the National Cancer Institute's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). *J Natl Cancer Inst* 2014;106:1–11.
- Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med* 2014;371:424–33.

- Bellmunt J, Théodore C, Demkov T, et al. Phase III trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract. *J Clin Oncol* 2009;27:4454–61.
- Blank C, Gajewski TF, Mackensen A. Interaction of PD-L1 on tumor cells with PD-1 on tumor-specific T cells as a mechanism of immune evasion: implications for tumor immunotherapy. *Cancer Immunol Immunother* 2005;54:307–14.
- Blank C, Mackensen A. Contribution of the PD-L1/PD-1 pathway to T-cell exhaustion: an update on implications for chronic infections and tumor evasion. *Cancer Immunol Immunother* 2007;56:739–45.
- Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med* 2015;373:1627–39.
- Brooks R. EuroQoL: the current state of play. *Health Policy* 1996; 37:53–72.
- Butte MJ, Keir ME, Phamduy TB. Programmed death-1 ligand 1 interacts specifically with the B7-1 costimulatory molecule to inhibit T cell responses. *Immunity* 2007;27:111–22.
- Caffo O, De Giorgi U, Fratino L, et al. Clinical outcomes of castration-resistant prostate cancer treatments administered as third or fourth line following failure of docetaxel and other second-line treatment: results of an Italian multicentre study. *Eur Urol* 2015;68:147–53.
- Cheever MA, Higano CS. PROVENGE (Sipuleucel-T) in prostate cancer: the first FDA-approved therapeutic cancer vaccine. *Clin Cancer Res* 2011;17:3520–6.
- Chen DS, Irving BA, Hodi FS. Molecular pathways: next-generation immunotherapy-inhibiting programmed death-ligand 1 and programmed death-1. *Clin Cancer Res* 2012;18:6580–7.
- Chi K, Kheoc T, Ryan C, et al. A prognostic index model for predicting overall survival in patients with metastatic castration-resistant prostate cancer treated with abiraterone acetate after docetaxel. *Ann Oncol* 2016;27:454–60.
- Choueiri TK, Ross RW, Jacobus S, et al. Double-blind, randomized trial of docetaxel plus vandetanib versus docetaxel plus placebo in platinum-pretreated metastatic urothelial cancer. *J Clin Oncol* 2012;30:507–12.
- Chung KC, PharmD MS, Barlev A, et al. Assessing analgesic use in patients with advanced cancer: Development of a new scale—the Analgesic Quantification Algorithm. *Pain Med* 2014;15:225–32.
- Cleeland C. The brief pain inventory (BPI): User guide. 2009.
- Cleeland CS, Body J-J, Stopeck A, et al. Pain outcomes in patients with advanced breast cancer and bone metastases. Results from a randomized, double-blind study of denosumab and zoledronic acid. *Cancer* 2013;119:832–8.

- de Bono JS, Chowdhury S, Feyerabend S, et al. Efficacy and safety of enzalutamide (ENZA) in patients with metastatic castration-resistant prostate cancer (mCRPC) previously treated with abiraterone acetate (Abi): A multicenter, single-arm, open-label study [abstract]. *J Clin Oncol* 2017;35:165.
- de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet Oncol* 2010;376:1147–54.
- de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med* 2011;364:1995–2005.
- DeMets D, Lan KKG. Interim analysis: the alpha spending function approach. *Stat Med* 1994;13:1341–52.
- Donahue RN, Madan RA, Richards Jacob, et al. Short-course enzalutamide reveals immune activating properties in patients with biochemically recurrent prostate cancer. In: *Proc AACR; 2016. Abstract 4901.*
- Drake CG, Doody ADH, Mihalyo MA, et al. Androgen ablation mitigates tolerance to a prostate/prostate cancer-restricted antigen. *Cancer Cell* 2005;7:239–49.
- Ellis LM, Bernstein DS, Voest EE, et al. American Society of Clinical Oncology perspective: raising the bar for clinical trials by defining clinically meaningful outcomes. *J Clin Oncol* 2014;32:1277–80.
- European Medicines Agency. Guideline on the evaluation of anticancer medicinal products in man. 2012 Dec. EMA/CHPM/205/95/Rev.4.
- Fayers P, Aaronson K, Bjordal M, et al. EORTC Quality of Life-C30 scoring manual. 2001;EORTC Quality of Life Group, Brussels.
- [FDA] U.S. Department of Health and Human Services Food and Drug Administration. Guidance for industry: clinical trial endpoints for the approval of cancer drugs and biologics. 2007 May.
- Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. *Lancet* 2016;387:1837–46.
- Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: <http://globocan.iarc.fr>, accessed on 15 July 2016.
- Fizazi K, Tran N, Fein L, et al. Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer. *N Engl J Med* 2017:1–9. [Epub ahead of print].

- Fizazi K, Scher HI, Miller K, et al. Effect of enzalutamide on time to first skeletal-related event, pain, and quality of life in men with castration-resistant prostate cancer: results from the randomized, Phase 3 AFFIRM trial. *Lancet Oncol* 2014a;15:1147–56.
- Flaig TW, Potluri RC, NG Y, et al. Treatment evolution for metastatic castration-resistant prostate cancer with recent introduction of novel agents: retrospective analysis of real-world data. *Cancer Med* 2015;5:182–91.
- Fozza C, Corda G, Viridis P, et al. Derangement of the T-cell repertoire in patients with B-cell non-Hodgkin's lymphoma. *Eur J Haematol* 2014:1–12.
- Galand C, Donnou S, Molina TJ, et al. Influence of tumor location on the composition of immune infiltrate and its impact on patient survival. Lessons from DCBCL and animal models. *Front Immunol* 2012;3:1–8.
- Gannon PO, Poisson AO, Delvoye N, et al. Characterization of the intra-prostatic immune cell infiltration in androgen-deprived prostate cancer patients. *J Immunol Methods* 2009;348:9–17.
- Garcia JA, Dreicer R. Systemic chemotherapy for advanced bladder cancer: update and controversies. *J Clin Oncol* 2006;24:5545–51.
- Gevensleben H, Dietrich D, Golletz C, et al. The immune checkpoint regulator PD-L1 is highly expressed in aggressive primary prostate cancer. *Clin Cancer Res*. 2016;22:1969–77.
- Glimm E, Maurer W, Bretz F. Hierarchical testing of multiple endpoints in group-sequential trials. *Stat Med* 2010;29:219–28.
- Graff JN, Alumkal JJ, Drake CG, et al. Early evidence of anti-PD-1 activity in enzalutamide-resistant prostate cancer. *Oncotarget* 2016;doi:10.18632/oncotarget.10547
- Guerrero J, Alfaro IE, Gomez F, et al. Enzalutamide, an androgen receptor signaling inhibitor, induces tumor regression in a mouse model of castration-resistant prostate cancer. *Prostate* 2013;73:1291–305.
- Halabi S, Lin CY, Kelly K, et al. Updated prognostic model for predicting overall survival in first-line chemotherapy for patients with metastatic castration-resistant prostate cancer. *J Clin Oncol* 2014;32:671–7.
- Hales RK, Banchereau J, Ribas A, et al. Assessing oncologic benefit in clinical trials of immunotherapy agents. *Ann Oncol* 2010;21:1944–51.
- Harland S, Staffurth J, Molina A, et al. Effect of abiraterone acetate treatment on the quality of life of patients with metastatic castration-resistant prostate cancer after failure of docetaxel chemotherapy. *Eur J Cancer* 2013;49:3648–57.
- Harris V, Lloyd K, Forsey S, et al. A population-based study of prostate cancer chemotherapy. *Clin Oncol* 2011;23:706–8.

- Heidenreich A, Bastian PJ, Bellmunt J, et al. EAU guidelines on prostate cancer. Part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer. *Eur Urol* 2014;65:467–79.
- Herbst RS, Soria JC, Kowanetz M et al. Predictive correlates of response to the anti-PD-L1 antibody atezolizumab in cancer patients. *Nature* 2014; 515: 563–7.
- Herbst RS, Baas P, Kim D-W, et al. Pembrolizumab versus docetaxel for previously treated PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet* 2016;387;1540–50.
- Herdman M, Gudex C, Lloyd A et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011;20:1727–36.
- Hodi FS, O’Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med* 2010;363:711–23.
- Hung HM, Wang SJ, O’Neil R. Statistical considerations for testing multiple endpoints in group sequential or adaptive clinical trials. *J Biopharm Stat* 2007;14:1201–10.
- James ND, de Bono JS, Spears MR, et al. Abiraterone for prostate cancer not previously treated with hormone therapy. *N Engl J Med* 2017:1–13. [Epub ahead of print].
- James ND, Sydes MR, Clarke NW, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. *Lancet* 2016;387:1163–77.
- Janssen MF, Pickard AS, Golicki D, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. *Qual Life Res* 2013;22:1717–27.
- Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med* 2010;363:411–22.
- Keir ME, Butte MJ, Freeman GJ, et al. PD-1 and its ligands in tolerance and immunity. *Annual Rev Immunol* 2008;26:677–704.
- Kirby M, Hirst C, Crawford ED. Characterising the castration-resistant prostate cancer population: a systematic review. *Int J Clin Pract* 2011;65:1180–92.
- Koh YT, Gray A, Higgins SA, Hubby B, Kast WM. Androgen ablation augments prostate cancer vaccine immunogenicity only when applied after immunization. *Prostate* 2009;69:571–84.
- Kwilas AR, Ardiani A, Dimeier U, et al. A poxviral-based cancer vaccine the transcription factor twist inhibits primary tumor growth and metastases in a model of metastatic breast cancer and improves survival in a spontaneous prostate cancer model. *Oncotarget* 2015;6:28194–210.

- Kwon ED, Drake CG, Scher HI, et al. Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): a multicentre, randomised, double-blind, phase 3 trial. *Lancet Oncol* 2014;15:700–12.
- Lafeuille MH, Gravel J, Grittner A, et al. Real-world corticosteroid utilization patterns in patients with metastatic castration-resistant prostate cancer in 2 large US administrative claims disease. *Am Health Drug Benefits* 2013;6:307–16.
- Laporte S, Squifflet P, Baroux N, et al. Prediction of survival benefits from progression-free survival benefits in advanced non-small cell lung cancer: evidence from a meta-analysis of 2334 patients from 5 randomized trials. *BMJ Open* 2013;3:1–6.
- Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. *Biol Blood Marrow Transplant* 2019;25:625–38.
- Li Z, Bishop AC, Alyamani M, et al. Conversion of abiraterone to D4A drives antitumor activity in prostate cancer. *Nature* 2015;523:347–51.
- Lissbrant IF, Garmo H, Widmark A, Stattin P. Population-based study on use of chemotherapy in men with castration resistant prostate cancer. *Acta Oncol* 2013;52:1593–601.
- Logothetis CJ, Basch E, Molina A, et al. Effect of abiraterone acetate and prednisone compared with placebo and prednisone on pain control and skeletal-related events in patients with metastatic castration-resistant prostate cancer: exploratory analysis of data from COU-AA-301 randomised trial. *Lancet Oncol* 2012;13:1210–7.
- Malvezzi M, Bertuccio P, Levi F, et al. European cancer mortality predictions for the year 2013. *Ann Oncol* 2013;00:1–9.
- Massari F, Ciccarese C, Calìò A, et al. Magnitude of PD-1, PD-L1 and T lymphocyte expression on tissue from castration-resistant prostate adenocarcinoma: An exploratory analysis. *Target Oncol* 2016;11:345–51.
- McClain KL, Eckstein O. *Clinical features and diagnosis of hemophagocytic lymphohistiocytosis. Up to Date [resource on the Internet]. 2014 [updated 29 October 2018; cited: 17 May 2019]. Available from: <https://www.uptodate.com/contents/clinical-features-and-diagnosis-of-hemophagocytic-lymphohistiocytosis>.*
- Mercader M, Bodner BK, Moser MT, et al. T cell infiltration of the prostate induced by androgen withdrawal in patients with prostate cancer. *Proc Natl Acad Sci USA* 2001;98:14565–70.
- Merritt RE, Mahtabifard A, Yamada RE, et al. Cisplatin augments cytotoxic T-lymphocyte-mediated antitumor immunity in poorly immunogenic murine lung cancer. *J Thorac Cardiovasc Surg* 2003;126:1609–17.



- Miller VA, Hirsh V, Cadranet J, et al. Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial. *Lancet Oncol* 2012;12:528–38.
- Mohler JL, Armstrong AJ, Bahnson RR, et al. Prostate Cancer, Version 1. 2016. *J Natl Compr Canc Netw* 2016;14:19–30.
- Morse MD, McNeel DG. Prostate cancer patients on androgen deprivation therapy develop persistent changes in adaptive immune responses. *Hum Immunol* 2010;71:496–504.
- Nesslinger, NJ, Sahota RA, Stone B, et al. Standard treatments induce antigen-specific immune responses in prostate cancer. *Clin Cancer Res* 2007;13:1493–502.
- Onukwugha E, Mullins CD, Hsu VD, Seal B, Hussain A. effect of urologists and medical oncologists on treatment of elderly men with stage IV prostate cancer. *Urology* 2011;77:1088–95.
- Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med* 2013;369:213–23.
- Parker C, Gillessen S, Heidenreich A et al. Cancer of the prostate: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2015;26(Suppl 5):v69–v77
- Petrylak DP, Tangen CM, Hussain MH, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med* 2004;351:1513–20.
- Pezaro CJ, Omlin A, Lorente D, et al. Visceral disease in castration-resistant prostate cancer. *Eur Urol* 2013;65:270–3.
- Postow M, Manuel M, Wong P, et al. T cell receptor diversity evaluation to predict patient response to ipilimumab in metastatic melanoma. *J Immunother Cancer* 2014;2(Suppl 3):08.
- Powderly JD, Koeppen H, Hodi FS, et al. Biomarkers and associations with the clinical activity of PD-L1 blockade in a atezolizumab study. *J Clin Oncol* 2013;31:abstract 3001.
- Ravelli A, Minoia F, Davi S, et al. 2016 classification criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a European League Against Rheumatism/American College of Rheumatology/Paediatric Rheumatology International Trials Organisation Collaborative Initiative. Ann Rheum Dis 2016;75:481–9.*
- Riegler LL, Jones GP, Lee DW. Current approaches in the grading and management of cytokine release syndrome after chimeric antigen receptor T-cell therapy. Ther Clin Risk Manag 2019;15:323–35.114*

- Roden AC, Moser MT, Tri SD, et al. Augmentation of T cell levels and responses induced by androgen deprivation. *J Immunol* 2004;173:6098–108.
- Romanel A, Gasi Tandefelt D, Conteduca V, et al. Plasma AR and abiraterone-resistant prostate cancer. *Sci Transl Med* 2015;7:312re10.
- Roodman GD. Mechanisms of bone metastasis. *N Engl J Med* 2004;350:1655–64.
- Rosenberg JE, Hoffman-Censits J, Powles T, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. *Lancet* 2016;387:1909–20.
- Rossille D, Gressier M, Damotte D, et al. High level of soluble programmed cell death ligand 1 in blood impacts overall survival in aggressive diffuse large B-cell lymphoma: results from a French multicenter clinical trial. *Leukemia* 2014;28:2367–75.
- Rotz SJ, Leino D, Szabo S, et al. Severe cytokine release syndrome in a patient receiving PD-1-directed therapy. *Pediatr Blood Cancer* 2017;64:e26642.*
- Roviello G, Petrioli R, Laera L, Francini E. The third line of treatment for metastatic prostate cancer patients: options or strategy? *Crit Rev Oncol Hematol* 2015;95:265–71.
- Ryan CJ, Smith MR, de Bono JS, et al. Randomized phase 3 trial of abiraterone acetate in men with metastatic castration-resistant prostate cancer and no prior chemotherapy. *N Engl J Med* 2013;368:138–48.
- Sandler A, Gray R, Perry MC, et al. Paclitaxel–carboplatin alone or with bevacizumab for non–small-cell lung cancer. *N Engl J Med* 2006;355:2542–50.
- Scher H, Halabi S, Tannock I, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. *J Clin Oncol* 2008;26:1148–59.
- Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med* 2012 Sep 27;367:1187–97.
- Scher HI, Morris MJ, Stadler WM, et al. Trial design and objectives for castration-resistant prostate cancer: updated recommendations from the prostate cancer clinical trials working group 3. *J Clin Oncol* 2016;34:1402–18.
- Schweizer M, Drake CG. Immunotherapy for prostate cancer-recent developments and future challenges. *Cancer Metastasis Rev* 2014;33:641–655.
- Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *Ca Cancer J Clin* 2016;66:7–30.
- Sonpavde G, Sternberg CN, Rosenberg JE, et al. Second-line systemic therapy and emerging drugs for metastatic transitional-cell carcinoma of the urothelium. *Lancet Oncol* 2010;11:861–70.

- Sternberg CN, Molina A, North S, et al. Effect of abiraterone acetate on fatigue in patients with metastatic castration-resistant prostate cancer after docetaxel chemotherapy. *Annals of Oncology* 2013;24:1017–1025.
- Stinchcombe TE, Socinski MA, Lee CB, et al. Considerations for second-line therapy of non-small cell lung cancer. *Oncologist* 2008;13:128–36.
- Sutherland JS, Goldberg GL, Hammet MV, et al. Activation of thymic regeneration in mice and humans following androgen blockade. *J Immunol* 2005;175:2741–53.
- Sweeney GJ, Chen YH, Carducci M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. *N Engl J Med* 2015;373:737–746.
- Tannock, IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med* 2004;351:1502–1512.
- Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. *New Engl J Med* 2010;363:733–42.
- The EuroQoL Group. EuroQoL—a new facility for the measurement of health-related quality of life. *Health Policy* 1990;16:199–208.
- Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med* 2012;366:2443–54.
- van Andel G, Bottomley A, Fosså SD, et al. An international field study of the EORTC QLQ-PR25: a questionnaire for assessing the health-related quality of life of patients with prostate cancer. *Eur J Cancer* 2008;44:2418–24.
- van Soest RJ, van Royen ME, de Morrée ES, et al. Cross-resistance between taxanes and new hormonal agents abiraterone and enzalutamide may affect drug sequence choices in metastatic castration-resistant prostate cancer. *Eur J Cancer* 2013;49:3821–30.
- Viselli SM, Stanziale S, Shults K, Kovacs WJ, Olsen NJ. Castration alters peripheral immune function in normal male mice. *Immunol* 1995;84:337–342.
- Westfall PH, Krishen A. Optimally weighted, fixed sequence and gatekeeper multiple testing procedures. *J Stat Plan Inf* 2001;99:25–40.
- Yang J, Riella LV, Chock S. The novel costimulatory programmed death ligand 1/B7.1 pathway is functional in inhibiting alloimmune responses in vivo. *J Immunol* 2011;187:1113–9.

## Appendix 1 Schedule of Activities

	Screening <sup>a</sup>	Treatment (Each cycle=21 days)	Treatment Discontinuation (≤30 Days) <sup>b</sup>	Safety Visit <sup>c</sup> (120 Days ±30 Days)	Study Termination <sup>d</sup>
	Days -28 to -1	Day 1 (± 3 Days for Cycles ≥2)			
Informed consent <sup>a</sup>	x				
Medical, surgical, and cancer histories and baseline conditions, including demographic information <sup>e</sup>	x				
Viral serology <sup>f</sup>	x				
Concomitant medications <sup>g</sup>	x	x	x		
Opiate analgesics use for cancer pain <sup>h</sup>	x	x			
Tumor assessment <sup>i</sup>	x	Every 9 weeks (±3 days) for the first 27 weeks and every 12 weeks (±6 days) thereafter until confirmed radiographic disease progression, death, or loss of follow-up			
Complete physical examination <sup>j</sup>	x		x		
Limited physical examination <sup>k</sup>		x <sup>l</sup>		x	
ECOG performance status	x	x <sup>l</sup>	x	x	
Vital signs <sup>m</sup>	x	x			
Electrocardiogram <sup>n</sup>	x	x <sup>n</sup>	x		
Echocardiogram <sup>n</sup>	x				
Weight	x		x	x	
Height	x				
Hematology <sup>o</sup>	x	x <sup>l</sup>	x	x	
Serum chemistry <sup>p</sup>	x	x <sup>l</sup>	x	x	

## Appendix 1 Schedule of Activities (cont.)

	Screening <sup>a</sup>	Treatment (Each Cycle = 21 days)	Treatment Discontinuation (≤ 30 Days) <sup>b</sup>	Safety Visit <sup>c</sup> (120 Days ± 30 Days)	<i>Study Termination</i> <sup>d</sup>
	Days -28 to -1	Day 1 (± 3 Days for Cycles ≥ 2)			
Coagulation panel (INR, and aPTT or PTT) <sup>q</sup>	x		x	x	
TSH, free T3, free T4 <sup>r</sup>	x	x <sup>l</sup>	x	x	
Autoantibody testing	x				
Testosterone	x				
Historic values for PSA velocity <sup>s</sup>	x				
PSA <sup>t</sup>	x	x	x	x <sup>t</sup>	x <sup>t</sup>
Archival and/or fresh FFPE tumor tissue specimen or 15 unstained slides <sup>u</sup>	x				
Tumor biopsy <sup>v</sup>		At the time of confirmed radiographic progression			

## Appendix 1 Schedule of Activities (cont.)

	Screening <sup>a</sup>	Treatment (Each Cycle = 21 days)	Treatment Discontinuation (≤ 30 Days) <sup>b</sup>	Safety Visit <sup>c</sup> (120 Days ± 30 Days)	Study Termination <sup>d</sup>
	Days -28 to -1	Day 1 (± 3 Days for Cycles ≥ 2)			
Symptomatic skeletal events <sup>w</sup>			x		
Atezolizumab infusion <sup>x</sup>		x			
Enzalutamide treatment <sup>y</sup>		x			
Adverse events <sup>z</sup>	x		x		
Survival and anti-cancer therapy follow-up <sup>d</sup>				x	x

ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; FFPE = formalin fixed paraffin embedded; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; IV = intravenous; PCWG3 = Prostate Cancer Working Group 3; PD-L1 = programmed death-ligand 1; RECIST = Response Evaluation Criteria in Solid Tumors; SSE = symptomatic skeletal event; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone.

Notes: Assessments scheduled on the days of study treatment infusions should be performed before the infusion unless otherwise noted.

- <sup>a</sup> Written informed consent is required for performing any study-specific tests or procedures. Signing of the Informed Consent Form can occur outside the 28-day screening period. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to study entry (except where otherwise specified) may be used for screening assessments rather than repeating such tests. If re-screening is required, then HBV, HCV, HIV, and autoantibody testing from the initial screening may be acceptable for screening assessment if performed < 60 days from Cycle 1 Day 1.
- <sup>b</sup> Patients will be asked to return to the clinic not more than 30 days after the last study treatment for a treatment discontinuation visit.
- <sup>c</sup> Patients will be asked to return to the clinic 120 days ± 30 days after the last study treatment for a safety visit. Only patients taking atezolizumab are required to return for the safety visit.
- <sup>d</sup> All patients will be followed for survival until study termination unless the patient requests to be withdrawn from the study; this request must be documented in the source documents and signed by the investigator. If the patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only.
- <sup>e</sup> Cancer history includes stage, date of diagnosis, and prior anti-tumor treatment. Demographic information includes age, sex, and self-reported race/ethnicity. Smoking history should also be captured.

## Appendix 1 Schedule of Activities (cont.)

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- <sup>f</sup> At screening, patients will be tested for HIV, HBsAg, HBsAb, total HBcAb, and HCV antibody. If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test should be performed. If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an active HCV infection.
- <sup>g</sup> Concomitant medications include any prescription medications or over-the-counter medications. At screening, any medications the patient has used within the 7 days prior to initiation of study treatment should be documented. At subsequent visits, changes to current medications or medications used since the last documentation of medications will be recorded.
- <sup>h</sup> At screening, any opiate analgesic medications a patient has used within the 7 days prior to initiation of study treatment should be documented.
- <sup>i</sup> Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days of Cycle 1, Day 1 may be used rather than repeating tests. All measurable and evaluable lesions should be assessed and documented at the screening visit. The same radiographic procedure must be used throughout the study for each patient. Results must be reviewed by the investigator before dosing at the next cycle. Tumor assessments will be performed at baseline, every 9 weeks (approximately every three cycles) following randomization for 27 weeks, and every 12 weeks thereafter, with additional scans as clinically indicated. Assessments will continue until confirmed radiographic disease progression per PCWG3 criteria. For patients who continue to receive study treatment following confirmed disease progression, assessments will continue until loss of clinical benefit. If an optional biopsy is to be performed at approximately the same time point of a tumor assessment or as a result of the radiographic determination (e.g., response or progression), samples should be acquired after all imaging scans have been performed, if at all possible. Once patients discontinue study treatment, tumor assessments should no longer be performed as per this study, and should be performed as per standard of care as determined by the investigator.
- <sup>j</sup> Complete physical examination includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF.
- <sup>k</sup> Perform a limited, symptom-directed examination at specified timepoints or as clinically indicated. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.
- <sup>l</sup> ECOG performance status, limited physical examination, and local laboratory assessments may be obtained  $\leq 4$  days before Day 1 of each cycle.
- <sup>m</sup> Vital signs include heart rate, respiratory rate, blood pressures, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. Vital signs should be measured at every cycle for all patients. Vital signs should be measured within 60 minutes prior to each atezolizumab infusion and, if clinically indicated, during or after the infusion.
- <sup>n</sup> ECG recordings will be obtained as part of the screening assessment, at Day 1 of Cycle 4 and every 4 cycles thereafter during treatment, at the end of treatment visit, and when clinically indicated. ECGs will be reviewed by the investigator to determine patient eligibility at screening. Baseline evaluation of left ventricular ejection fraction should be considered for all patients, especially in those with cardiac risk factors and/or history of coronary artery disease. For patients with a history of clinically significant cardiac disease (including anatomic abnormality, coronary disease, congestive heart failure, abnormal LVEF, arrhythmia, or abnormal ECG) will be required to undergo a screening echocardiogram.

## Appendix 1 Schedule of Activities (cont.)

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- ° Hematology consists of CBC, including RBC count, hemoglobin, hematocrit, WBC count with automated differential (neutrophils, lymphocytes, eosinophils, monocytes, basophils, and other cells), and platelet count. A manual differential can be done if clinically indicated. Absolute neutrophil count, lymphocyte count, platelet count, and hemoglobin for study inclusion-related tests must be obtained 14 days prior to initiation of study treatment.
- ° Serum chemistry includes BUN or urea, creatinine, sodium, potassium, magnesium, chloride, bicarbonate, calcium, phosphorus, glucose, total bilirubin, ALT, AST, alkaline phosphatase, lactate dehydrogenase, total protein, and albumin. In countries where serum bicarbonate is not considered a standard chemistry measurement (e.g., Japan), serum bicarbonate is not required as a laboratory study in the screening or on-study serum measurements. AST, ALT, bilirubin, creatinine, and albumin for study inclusion-related tests must be obtained 14 days prior to initiation of study treatment.
- ° Coagulation panel for study inclusion-related tests must be obtained 14 days prior to initiation of study treatment.
- ° TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed on Day 1 of Cycle 1 and every fourth cycle thereafter.
- ° At least two PSA samples (obtained at least 1 week apart) will be assessed locally at screening. Samples analyzed prior to screening do not have to be repeated. Historic values of PSA will be collected to calculate PSA velocity.
- ° The PSA sample will be assessed locally. PSA should be performed as per standard of care once patient discontinues study treatment.
- ° After signing the Informed Consent Form, retrieval and submission of archival tumor sample can occur more than 28 days prior to start of study treatment but must be submitted prior to enrollment. Tissue samples will not be collected for patients in the safety run-in phase. See Section 4.5.6 for tissue sample requirements.
- ° Tumor specimens are recommended at the time of confirmed radiographic disease progression per PCWG3 criteria, unless the location of the tumor renders the biopsy medically unsafe or infeasible per investigator decision. Biopsies should be performed within 40 days after progression or prior to the next anti-cancer therapy, whichever is sooner. See Section 4.5.6 for tissue sample requirements. Preferably, growing lesions should be selected.
- ° An SSE is defined as external beam radiation therapy to relieve skeletal symptoms (including initiation of radium-223 dichloride or other types of radionuclide therapy to treat symptoms of bone metastases), new symptomatic pathologic bone fracture, clinically apparent occurrence of spinal cord compression, or tumor related orthopedic surgical intervention
- ° The initial dose of atezolizumab will be delivered over 60 ( $\pm$  15) minutes. If the first infusion is tolerated without infusion-associated adverse events, the second infusion may be delivered over 30 ( $\pm$  10) minutes. If the 30-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 ( $\pm$  10) minutes.
- ° Enzalutamide will be administered at a dose of 160 mg orally once daily. Study drug doses should be taken as close as possible to the same time each day. The study drug can be taken with or without food.



## **Appendix 1 Schedule of Activities (cont.)**

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<sup>z</sup> After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until 30 days after the last dose of study drug or initiation of another systemic anti-cancer therapy, whichever occurs first and serious adverse events and adverse events of special interest will be reported until 90 days after the last dose of study drug or initiation of another systemic anti-cancer therapy, whichever occurs first. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study treatment. The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or study-related procedures until a final outcome can be reported.

## Appendix 2

### Criteria for Radiographic Progression per Prostate Cancer Working Group 3

Date Progression Detected (Visit) <sup>a</sup>	Criteria for Progression	Criteria for Confirmation of Progression (requirement and timing)	Criteria for Documentation of Disease Progression on Confirmatory Scan
Week 9	Bone lesions: Two or more new lesions compared to <b>baseline</b> bone scan by PCWG3 Soft tissue lesions: Progressive disease on CT or MRI by modified RECIST v1.1 <sup>b</sup>	Timing: at least 6 weeks after progression identified or at Week 18 visit. <sup>c</sup> No confirmatory scan required for soft tissue disease progression.	Two or more new bone lesions on bone scan (compared to Week 9 scan). NA
Week 18 or later	Bone lesions: Two or more new lesions on bone scan compared <b>to Week 9</b> bone scan Soft tissue lesions: Progressive disease on CT or MRI by modified RECIST v1.1 <sup>b</sup>	Timing: at least 6 weeks after progression identified. Required for bone lesions observed on bone scan <sup>c</sup> No confirmatory scan required for soft tissue disease progression.	Persistent <sup>d</sup> or increase in number of bone lesions on bone scan compared to prior scan. NA

CT= computed tomography; MRI=magnetic resonance imaging; NA=not applicable; PCWG3=Prostate Cancer Working Group 3, RECIST=Response Evaluation Criteria in Solid Tumors.

Note: Adapted from Scher et al. 2016.

<sup>a</sup> Progression detected by bone scan at an unscheduled visit will require a confirmatory scan at least 6 weeks later and should follow confirmation criteria outlined in the table for the next scheduled scan. Progression detected by bone scan at an unscheduled visit prior to Week 12 will require a confirmatory scan at least 6 weeks later showing two or more new bone lesions on bone scan.

<sup>b</sup> For RECIST v1.1 see [Appendix 3](#). Up to five lesions per site of spread will be recorded as target lesions (lung, liver, adrenal, nodal).

<sup>c</sup> Confirmation must occur at the next available scan.

<sup>d</sup> For confirmation, at least two of the lesions first identified as new must be present at that next available scan.

## **Appendix 3**

### **Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)**

Selected sections from the Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (Eisenhauer et al. 2009), are presented below, with slight modifications from the original publication and the addition of explanatory text as needed for clarity.<sup>1</sup>

#### **TUMOR MEASURABILITY**

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described below. All measurable and non-measurable lesions should be assessed at screening and at subsequent protocol-specified tumor assessment timepoints. Additional assessments may be performed as clinically indicated for suspicion of progression.

#### **DEFINITION OF MEASURABLE LESIONS**

##### **Tumor Lesions**

Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size as follows:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval  $\leq 5$  mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

##### **Malignant Lymph Nodes**

To be considered pathologically enlarged and measurable, a lymph node must be  $\geq 15$  mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be  $\leq 5$  mm). At baseline and follow-up, only the short axis will be measured and followed. Additional information on lymph node measurement is provided below (see "Identification of Target and Non-Target Lesions" and "Calculation of Sum of Diameters").

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<sup>1</sup> For clarity and for consistency within this document, the section numbers and cross-references to other sections within the article have been deleted and minor changes have been made.

## **Appendix 3 Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (cont.)**

### **DEFINITION OF NON-MEASURABLE LESIONS**

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with short axis  $\geq$  10 mm but < 15 mm) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

### **SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY**

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

#### **Bone Lesions:**

- Technetium-99m bone scans, sodium fluoride positron emission tomography scans, and plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

#### **Cystic Lesions:**

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

#### **Lesions with Prior Local Treatment:**

- Tumor lesions situated in a previously irradiated area or in an area subjected to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion.

## **Appendix 3 Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (cont.)**

### **METHODS FOR ASSESSING LESIONS**

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during the study. Imaging-based evaluation should always be the preferred option.

### **CLINICAL LESIONS**

Clinical lesions will only be considered measurable when they are superficial and  $\geq 10$  mm in diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is suggested.

### **CHEST X-RAY**

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

### **CT AND MRI SCANS**

CT is the best currently available and reproducible method to measure lesions selected for response assessment. In this guideline, the definition of measurability of lesions on CT scan is based on the assumption that CT slice thickness is  $\leq 5$  mm. When CT scans have slice thickness of  $> 5$  mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with intravenous (IV) contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease, and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point

## **Appendix 3 Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (cont.)**

forward. Care must be taken in measurement of target lesions and interpretation of non-target disease or new lesions on a different modality, since the same lesion may appear to have a different size using a new modality.

### **ENDOSCOPY, LAPAROSCOPY, ULTRASOUND, TUMOR MARKERS, CYTOLOGY, HISTOLOGY**

Endoscopy, laparoscopy, ultrasound, tumor markers, cytology, and histology cannot be utilized for objective tumor evaluation.

### **ASSESSMENT OF TUMOR BURDEN**

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements.

### **IDENTIFICATION OF TARGET AND NON-TARGET LESIONS**

When more than one measurable lesion is present at baseline, all lesions (a maximum of five lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Other lesions (albeit measurable) will be considered non-target lesions.

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, but in addition should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of  $\geq 15$  mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Lymph node size is normally reported as two dimensions in the plane in which the image is obtained (for CT, this is almost always the axial plane; for MRI, the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm  $\times$  30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis  $\geq 10$  mm

## **Appendix 3 Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (cont.)**

but < 15 mm) should be considered non-target lesions. Nodes that have a short axis of < 10 mm are considered non-pathological and should not be recorded or followed.

All lesions (or sites of disease) not selected as target lesions (measurable or non-measurable), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required. It is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (eCRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

### **CALCULATION OF SUM OF DIAMETERS**

A sum of the diameters (longest diameter for non-lymph node lesions, short axis for lymph node lesions) will be calculated for all target lesions at baseline and at each subsequent tumor assessment as a measure of tumor burden.

### **Measuring Lymph Nodes**

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the node regresses to < 10 mm during the study. Thus, when lymph nodes are included as target lesions, the sum of diameters may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm.

### **Measuring Lesions That Become Too Small to Measure**

During the study, all target lesions (lymph node and non-lymph node) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measurement and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the eCRF, as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.

## **Appendix 3**

### **Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (cont.)**

- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and "too small to measure" should be ticked. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and "too small to measure" should also be ticked).

To reiterate, however, if the radiologist is able to provide an actual measurement, that should be recorded, even if it is <5 mm, and in that case "too small to measure" should not be ticked.

#### **Measuring Lesions That Split or Coalesce on Treatment**

When non-lymph node lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the sum of diameters. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum longest diameter for the coalesced lesion.

#### **EVALUATION OF NON-TARGET LESIONS**

Measurements are not required for non-target lesions, except that malignant lymph node non-target lesions should be monitored for reduction to < 10 mm in short axis. Non-target lesions should be noted at baseline and should be identified as "present" or "absent" and (in rare cases) may be noted as "indicative of progression" at subsequent evaluations. In addition, if a lymph node lesion shrinks to a non-malignant size (short axis < 10 mm), this should be captured on the eCRF as part of the assessment of non-target lesions.

#### **RESPONSE CRITERIA**

##### **CRITERIA FOR TARGET LESIONS**

Definitions of the criteria used to determine objective tumor response for target lesions are provided below:

- CR: Disappearance of all target lesions  
Any pathological lymph nodes must have reduction in short axis to < 10 mm.
- PR: At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR



## **Appendix 3 Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (cont.)**

- Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters on study (including baseline)
  - In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of  $\geq 5$  mm.
- Stable disease (SD): Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD

### **CRITERIA FOR NON-TARGET LESIONS**

Definitions of the criteria used to determine the tumor response for the group of non-target lesions are provided below. Whereas some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the schedule of activities.

- CR: Disappearance of all non-target lesions and (if applicable) normalization of tumor marker level
  - All lymph nodes must be non-pathological in size ( $< 10$  mm short axis).
- Non-CR/Non-PD: Persistence of one or more non-target lesions and/or (if applicable) maintenance of tumor marker level above the normal limits
- PD: Unequivocal progression of existing non-target lesions

### **SPECIAL NOTES ON ASSESSMENT OF PROGRESSION OF NON-TARGET LESIONS**

#### **Patients with Measurable and Non-Measurable Disease**

For patients with both measurable and non-measurable disease to achieve unequivocal progression on the basis of the non-target lesions, there must be an overall level of substantial worsening in non-target lesions in a magnitude that, even in the presence of SD or PR in target lesions, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target lesions in the face of SD or PR in target lesions will therefore be extremely rare.

#### **Patients with Non-Measurable Disease Only**

For patients with non-measurable disease only, the same general concepts apply as noted above. However, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-measurable disease cannot be easily quantified (by definition, if all lesions are truly non-measurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease

### **Appendix 3 Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (cont.)**

burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease, that is, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from "trace" to "large" or an increase in lymphangitic disease from localized to widespread. If unequivocal progression is seen, the patient should be considered to have had overall PD at that point. Whereas it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

#### **NEW LESIONS**

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, progression should be declared using the date of the initial scan.

#### **CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT**

[Table 1](#) provides a summary of the overall response status calculation at each response assessment timepoint for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, [Table 2](#) is to be used.

### Appendix 3 Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (cont.)

**Table 1 Criteria for Overall Response at a Single Timepoint:  
Patients with Target Lesions (with or without Non-Target Lesions)**

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not all evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR=complete response; NE=not evaluable; PD=progressive disease; PR=partial response; SD=stable disease.

**Table 2 Criteria for Overall Response at a Single Timepoint:  
Patients with Non-Target Lesions Only**

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD <sup>a</sup>
Not all evaluated	No	NE
Unequivocal PD	Yes or no	PD
Any	Yes	PD

CR=complete response; NE=not evaluable; PD=progressive disease.

<sup>a</sup> "Non-CR/non-PD" is preferred over "stable disease" for non-target disease since stable disease is increasingly used as an endpoint for assessment of efficacy in some trials; thus, assigning "stable disease" when no lesions can be measured is not advised.

#### **MISSING ASSESSMENTS AND NOT-EVALUABLE DESIGNATION**

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If measurements are made on only a subset of target lesions at a timepoint, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesions would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and during the study only two lesions were assessed, but those

## **Appendix 3 Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (cont.)**

gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

### **SPECIAL NOTES ON RESPONSE ASSESSMENT**

Patients with a global deterioration in health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target lesions as shown in [Table 1](#) and [Table 2](#).

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

### **REFERENCES**

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228–47.

## Appendix 4

# European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire: EORTC QLQ-C30



### EORTC QLQ-C30 (version 3)

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

Please fill in your initials:

Your birthdate (Day, Month, Year):

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

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a <u>long</u> walk?	1	2	3	4
3. Do you have any trouble taking a <u>short</u> walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

#### During the past week:

	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

## Appendix 4

### European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire: EORTC QLQ-C30 (cont.)

ENGLISH

<b>During the past week:</b>	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 <u>family</u> life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your <u>social</u> 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 5

### European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire: Urinary Scale from EORTC QLQ-PR25



Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

	Not at All	A Little	Quite a Bit	Very Much
31. Have you had to urinate frequently during the day?	1	2	3	4
32. Have you had to urinate frequently at night?	1	2	3	4
33. When you felt the urge to pass urine, did you have to hurry to get to the toilet?	1	2	3	4
34. Was it difficult for you to get enough sleep because you needed to get up frequently at night to urinate?	1	2	3	4
35. Have you had difficulties going out of the house because you needed to be close to a toilet?	1	2	3	4
36. Have you had any unintentional release (leakage) of urine?	1	2	3	4
37. Did you have pain when you urinated?	1	2	3	4
39. Have your daily activities been limited by your urinary problems?	1	2	3	4

**Appendix 6**  
**EuroQol 5-Dimension Questionnaire: EQ-5D-5L**

**Health Questionnaire**

**English version for the USA**

Under each heading, please check the ONE box that best describes your health TODAY.

**MOBILITY**

- I have no problems walking
- I have slight problems walking
- I have moderate problems walking
- I have severe problems walking
- I am unable to walk

**SELF-CARE**

- I have no problems washing or dressing myself
- I have slight problems washing or dressing myself
- I have moderate problems washing or dressing myself
- I have severe problems washing or dressing myself
- I am unable to wash or dress myself

**USUAL ACTIVITIES** (e.g. work, study, housework, family or leisure activities)

- I have no problems doing my usual activities
- I have slight problems doing my usual activities
- I have moderate problems doing my usual activities
- I have severe problems doing my usual activities
- I am unable to do my usual activities

**PAIN/DISCOMFORT**

- I have no pain or discomfort
- I have slight pain or discomfort
- I have moderate pain or discomfort
- I have severe pain or discomfort



**Appendix 6**  
**EuroQoL 5-Dimension Questionnaire: EQ-5D-5L (cont.)**

I have extreme pain or discomfort

**ANXIETY/DEPRESSION**

I am not anxious or depressed

I am slightly anxious or depressed

I am moderately anxious or depressed

I am severely anxious or depressed

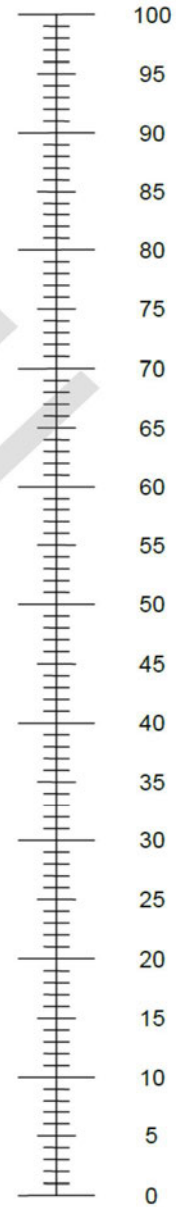
I am extremely anxious or depressed

## Appendix 6 EuroQol 5-Dimension Questionnaire: EQ-5D-5L (cont.)

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.  
0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =

The best health  
you can imagine



The worst health  
you can imagine

## Appendix 7 Pain Severity Assessments

### Pain Severity Assessment (Screening) from BPI-SF <sup>a</sup>

1. Please rate your pain by tapping the one number that best describes your pain at its **worst** in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

### Pain Severity Assessment (Day 1 of Cycle 1 and following Assessments) from BPI <sup>a</sup>

1. Please rate your pain by tapping the one number that best describes your pain at its **worst** in the last week.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

### 2. Tap the one number that describes how, during the past week, pain has interfered with your:

#### A. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

#### B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

#### C. Walking Ability

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

#### D. Normal Work (includes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

**Appendix 7**  
**Pain Severity Assessments (cont.)**

E. Relations with other people  
0      1      2      3      4      5      6      7      8      9      10  
Does not interfere      Completely interferes

F. Sleep  
0      1      2      3      4      5      6      7      8      9      10  
Does not interfere      Completely interferes

G. Enjoyment of life  
0      1      2      3      4      5      6      7      8      9      10  
Does not interfere      Completely interferes

<sup>a</sup> Questions from Brief Pain Inventory and Brief Pain Inventory-Short Form per author permission.

## Appendix 8 Analgesic Quantification Algorithm Score Categories and Equianalgesic Potency Conversions

### Analgesic Quantification Algorithm Score Categories

Score	Description
0	No analgesic
1	Non-opioid analgesics
2	Weak opioids (i.e., codeine and tramadol when not used in combination with other opioids)
3	Strong opioids $\leq$ 75 mg OME/day
4	Strong opioids > 75–150 mg OME/day
5	Strong opioids > 150–300 mg OME/day
6	Strong opioids > 300–600 mg OME/day
7	Strong opioids > 600 mg OME/day

OME=oral morphine equivalent.

## Appendix 8 Analgesic Quantification Algorithm Score Categories and Equianalgesic Potency Conversions (cont.)

### Equianalgesic Potency Conversions

Name	Equianalgesic Dose (mg)					
	IV	SC	IM	TM	PO	OME
Morphine	10	10	10	—	30	30
Fentanyl	0.1	0.1	0.1	0.1	2.4	30
Hydromorphone	1	1	1	—	5	20
Methadone	10	10	10	—	20	30
Oxycodone	10*	—	—	—	20	30
Hydrocodone	—	—	—	—	40	40
Codeine	120	120	120	—	200	30
Tramadol	100	100	100	—	100	30
Meperidine †	75	75	75	—	300	30
Buprenorphine	0.3	0.3	0.3	0.3	0.2	30
Butorphanol	—	—	2	—	—	30
Nalbuphine	10	10	10	—	—	30
Pentazocine	60	60	60	—	60	20

IV=intravenous; SC=subcutaneous; IM=intramuscular; TM=transdermal; OME=oral morphine equivalent; PO=oral.

\* Based on 1:2 ratio for IV to PO conversion as described by manufacturer.

† Based on Demystifying opioid conversions calculations: A guide for effective dosing. McPherson ML, 2009.

### **REFERENCE**

Adapted from Chung KC, PharmD MS, Barlev A, et al. Assessing analgesic use in patients with advanced cancer: Development of a new scale—the Analgesic Quantification Algorithm. Pain Med 2014;15:225–32.

## Appendix 9

### Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events

## NCI PRO-CTCAE™ ITEMS

### Item Library Version 1.0

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please check or mark an  in the one box that best describes your experiences over the past 7 days...

1.	In the last 7 days, what was the SEVERITY of your DECREASED APPETITE at its WORST?
	<input type="radio"/> None <input type="radio"/> Mild <input type="radio"/> Moderate <input type="radio"/> Severe <input type="radio"/> Very severe
	In the last 7 days, how much did DECREASED APPETITE INTERFERE with your usual or daily activities?
	<input type="radio"/> Not at all <input type="radio"/> A little bit <input type="radio"/> Somewhat <input type="radio"/> Quite a bit <input type="radio"/> Very much

2.	In the last 7 days, what was the SEVERITY of your CONSTIPATION at its WORST?
	<input type="radio"/> None <input type="radio"/> Mild <input type="radio"/> Moderate <input type="radio"/> Severe <input type="radio"/> Very severe

3.	In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA)?
	<input type="radio"/> Never <input type="radio"/> Rarely <input type="radio"/> Occasionally <input type="radio"/> Frequently <input type="radio"/> Almost constantly

4.	In the last 7 days, did you have any RASH?
	<input type="radio"/> Yes <input type="radio"/> No

5.	In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?
	<input type="radio"/> None <input type="radio"/> Mild <input type="radio"/> Moderate <input type="radio"/> Severe <input type="radio"/> Very severe
	In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?
	<input type="radio"/> Not at all <input type="radio"/> A little bit <input type="radio"/> Somewhat <input type="radio"/> Quite a bit <input type="radio"/> Very much

How much bothered were you with the side effect of your treatment?

Not at all       A little bit       Somewhat       Quite a bit       Very much

## Appendix 10 Preexisting Autoimmune Diseases

Subjects should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Subjects with any history of immune deficiencies or autoimmune disease listed in the table below are excluded from participating in the study. Possible exceptions to this exclusion could be subjects with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g., acute Lyme arthritis). Contact the Medical Monitor regarding any uncertainty over autoimmune exclusions.

### Autoimmune Diseases and Immune Deficiencies

<ul style="list-style-type: none"> <li>•Acute disseminated encephalomyelitis</li> <li>•Addison disease</li> <li>•Ankylosing spondylitis</li> <li>•Antiphospholipid antibody syndrome</li> <li>•Aplastic anemia</li> <li>•Autoimmune hemolytic anemia</li> <li>•Autoimmune hepatitis</li> <li>•Autoimmune hypoparathyroidism</li> <li>•Autoimmune hypophysitis</li> <li>•Autoimmune myocarditis</li> <li>•Autoimmune oophoritis</li> <li>•Autoimmune orchitis</li> <li>•Autoimmune thrombocytopenic purpura</li> <li>•Behçet disease</li> <li>•Bullous pemphigoid</li> <li>•Chronic fatigue syndrome</li> <li>•Chronic inflammatory demyelinating polyneuropathy</li> <li>•Churg-Strauss syndrome</li> <li>•Crohn disease</li> </ul>	<ul style="list-style-type: none"> <li>•Dermatomyositis</li> <li>•Diabetes mellitus type 1</li> <li>•Dysautonomia</li> <li>•Epidermolysis bullosa acquisita</li> <li>•Gestational pemphigoid</li> <li>•Giant cell arteritis</li> <li>•Goodpasture syndrome</li> <li>•Graves disease</li> <li>•Guillain-Barré syndrome</li> <li>•Hashimoto disease</li> <li>•IgA nephropathy</li> <li>•Inflammatory bowel disease</li> <li>•Interstitial cystitis</li> <li>•Kawasaki disease</li> <li>•Lambert-Eaton myasthenia syndrome</li> <li>•Lupus erythematosus</li> <li>•Lyme disease, chronic</li> <li>•Meniere syndrome</li> <li>•Mooren ulcer</li> <li>•Morphea</li> <li>•Multiple sclerosis</li> <li>•Myasthenia gravis</li> </ul>	<ul style="list-style-type: none"> <li>•Neuromyotonia</li> <li>•Opsoclonus myoclonus syndrome</li> <li>•Optic neuritis</li> <li>•Ord thyroiditis</li> <li>•Pemphigus</li> <li>•Pernicious anemia</li> <li>•Polyarteritis nodosa</li> <li>•Polyarthritits</li> <li>•Polyglandular autoimmune syndrome</li> <li>•Primary biliary cirrhosis</li> <li>•Psoriasis</li> <li>•Reiter syndrome</li> <li>•Rheumatoid arthritis</li> <li>•Sarcoidosis</li> <li>•Scleroderma</li> <li>•Sjögren's syndrome</li> <li>•Stiff-Person syndrome</li> <li>•Takayasu arteritis</li> <li>•Ulcerative colitis</li> <li>•Vitiligo</li> <li>•Vogt-Koyanagi-Harada disease</li> <li>•Wegener granulomatosis</li> </ul>
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## **Appendix 11 Anaphylaxis Precautions**

### **EQUIPMENT NEEDED**

- Tourniquet
- Oxygen
- Epinephrine for subcutaneous, intravenous, and/or endotracheal use in accordance with standard practice
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

### **PROCEDURES**

In the event of a suspected anaphylactic reaction during study treatment infusion, the following procedures should be performed:

1. Stop the study treatment infusion.
2. Apply a tourniquet proximal to the injection site to slow systemic absorption of study treatment. Do not obstruct arterial flow in the limb.
3. Maintain an adequate airway.
4. Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
5. Continue to observe the patient and document observations.

## Appendix 12

### Eastern Cooperative Oncology Group Performance Status Scale

Grade	Description
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework or office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about >50% of waking hours
3	Capable of only limited self-care, confined to a bed or chair >50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

## **Appendix 13**

### **Guidance on Reducing the Risks of Pharmacokinetic Drug–Drug Interactions with Enzalutamide**

For information on drug-drug interactions with enzalutamide, please see the local prescribing information.

There is a potential for other medicinal products to affect enzalutamide exposures and for enzalutamide to affect exposures to other medicinal products. Examples of drugs with the potential for drug-drug interactions with enzalutamide are provided below. For the most current list of drugs that may be subject to drug-drug interactions, consult the following sources:

- <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf>
- <http://medicine.iupui.edu/clinpharm/ddis/table.aspx>

#### **Potential for Other Medicinal Products to Affect Enzalutamide Exposures** **CYP2C8 inhibitors and inducers**

Clinical data indicate that CYP2C8 plays an important role in the metabolism of enzalutamide; therefore, strong inhibitors (e.g., gemfibrozil) or inducers (e.g., rifampicin) of CYP2C8 should be used with caution during enzalutamide treatment. If concomitant use of strong CYP2C8 inhibitors cannot be avoided, then the dose of study drug should be reduced to 80 mg per day (2 capsules).

#### **Potential for Enzalutamide to Affect Exposures to Other Medicinal Products** **Enzyme induction**

Clinical data indicate that enzalutamide is a strong inducer of CYP3A4 and a moderate inducer of CYP2C9 and CYP2C19. UGT may be induced as well. These results suggest that enzalutamide causes enzyme induction via activation of PXR. Medicinal products with a narrow therapeutic range that are substrates of CYP3A4, CYP2C9, CYP2C19, or UGT should be used with caution when administered concomitantly with enzalutamide and may require dose adjustment to maintain therapeutic plasma concentrations. Such substrates include, but are not limited to:

- Macrolide antibiotics (e.g., clarithromycin, doxycycline)
- Benzodiazepines (e.g., diazepam, midazolam, zolpidem)
- Immune modulators (e.g., cyclosporine, tacrolimus)
- HIV antivirals (e.g., indinavir, ritonavir)
- Anti-epileptics (e.g., carbamazepine, clonazepam, phenytoin, primidone, valproic acid)
- Coumarins (e.g., warfarin)

In consideration of the long half-life of enzalutamide (approximately 1 week), effects on enzymes may persist for 1 month or longer after stopping enzalutamide.

## **Appendix 13**

### **Guidance on Reducing the Risks of Pharmacokinetic Drug–Drug Interactions with Enzalutamide (cont.)**

#### **P-gp substrates**

In vitro data indicate that enzalutamide may be a P-gp inhibitor. The effects of enzalutamide on P-gp substrates have not been evaluated in vivo; however, under conditions of clinical use, enzalutamide may be an inducer of P-gp via activation of PXR. Medicinal products with a narrow therapeutic range that are substrates for P-gp (e.g., colchicine, dabigatran etexilate, digoxin) should be used with caution when administered concomitantly with enzalutamide and may require dose adjustment to maintain optimal plasma concentrations.