SAABR: Single Arm Phase II **S**tudy of **A**R targeted therapy + **A**tezolizumab + GnRH analog and Stereotactic **B**ody **R**adiotherapy (SBRT) to the Prostate in Men with Newly Diagnosed Hormone-sensitive Metastatic Prostate Cancer

Sponsor: Memorial Sloan Kettering Cancer Center (MSK)
CRO: Prostate Cancer Clinical Trials Consortium, LLC (PCCTC)
PCCTC #: c18-226

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APPROVAL OF PROTOCOL

Title**:** Single Arm Phase II Study of AR targeted therapy + Atezolizumab + GnRH analog and Stereotactic Body Radiotherapy (SBRT) to the Prostate in Men with Newly Diagnosed Hormone-sensitive Metastatic Prostate Cancer

Sponsor/Sponsor Principal Investigator Signature: _____
Print: _____
Date: _____

PCCTC Signature: _____
Print: _____
Date: _____

PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision and providing Memorial Sloan Kettering Cancer Center with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted Good Clinical Practice (GCP) principles, as adopted by applicable laws and regulations, and to abide by the terms of this protocol.

Principal Investigator Signature: _____

Principal Investigator Print: _____

Date: _____

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1. INTRODUCTION

1.1 Disease Background

In 2019, prostate cancer remains the most commonly diagnosed non-cutaneous malignancy and the second-leading cause of cancer death among men in the United States.[1] While radical local therapy with surgery or definitive radiation yield favorable outcomes and cure in men with localized prostate cancer, androgen deprivation therapy (ADT), the standard-of-care therapy for newly-diagnosed metastatic hormone-sensitive prostate cancer (mHSPC) only delays progression in this ultimately lethal state of prostate cancer.[2]

Recently, however, several large phase III trials have demonstrated that the addition of chemotherapy or a second-generation antiandrogen to ADT offers an additional survival benefit for men with mHSPC.[3-9]Moreover, outcomes in patients with locally advanced disease enrolled on one of these trials suggest that prostate radiation therapy is associated with a significant reduction in treatment failure.[4] Further, preclinical studies have shown that a type of very high-dose radiation, stereotactic body radiation therapy (SBRT), can induce an immunogenic effect through several different biological mechanisms including enhanced expression of the PD-L1 protein on both tumor and immune cells.[10,11] Therefore, combining androgen ablation (ADT + AR targeted therapy) with the cytotoxic and immune properties of SBRT, and the additional effects of atezolizumab, an anti-PD-L1 immunotherapy, is a new treatment approach with possible synergistic effects.

1.2 Atezolizumab Background

Atezolizumab is a humanized immunoglobulin (Ig) G1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity.[12,13] Atezolizumab has minimal binding to Fc receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

Atezolizumab shows anti-tumor activity in both nonclinical models and cancer patients 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 patients with locally advanced or metastatic urothelial carcinoma (mUC) who fit the following criteria: 1) are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 5% of the tumor area), as determined by a US Food and Drug Administration (FDA) approved test, or 2) are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status, or 3) have disease progression during or following any platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant chemotherapy.[14] Atezolizumab is also approved the treatment of previously treated locally advanced or metastatic non-small cell lung cancer (NSCLC),[15] extensive-stage small cell lung cancer (SCLC),[16] and triple-negative breast cancer (TNBC).[17]

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

1.3 Rationale

For decades, ADT with gonadotropin-releasing hormone (GnRH) analogues such as Lupron (leuprolide) has been a standard-of-care for newly-diagnosed mHSPC. Recently, large phase III randomized trials, including CHAARTED,[3,18] LATITUDE,[6] STAMPEDE,[4,7] ARCHES,[8] and ENZAMET[9] have demonstrated that the addition of docetaxel, AA, or enzalutamide to ADT offers a survival benefit for men with mHSPC relative to conventional ADT alone. These data have ushered in a new paradigm of treatment intensification in mHSPC. Despite these advances, men continue to develop castration-resistance and succumb to their disease.[19]

Notably, and in contrast to the localized setting, the primary prostate tumor remains untreated in *de novo* mHSPC. Subset analysis of subjects with locally advanced disease enrolled on STAMPEDE suggests that prostate radiation therapy is associated with a significant reduction in treatment failure events.[7,20] These data have led to the intriguing hypothesis that local treatment of the prostate in the metastatic setting may further improve outcomes in an era of more effective systemic hormonal therapy. Accordingly, the role of radical prostatectomy or radiation therapy in mHSPC is under active investigation in the ongoing Metacure (NCT03436654), PEACE1 (NCT01957436), and SWOG 1802 (NCT03678025) trials and radiotherapy arm of the MRC STAMPEDE (NCT00268476) trial.[21]

The evolution of SBRT has dramatically altered the treatment landscape for localized prostate cancer.[22] Hypofractionated (high dose per fraction) SBRT regimens are increasingly utilized, given that highly effective, safe, and convenient definitive treatment is delivered in only five fractions (7.25 Gy-8 Gy x 5). Recent preclinical data suggests that hypofractionated doses (i.e., 7-10 Gy per fraction) are particularly immunogenic and synergize effectively with immune checkpoint blockade (ICB), leading to excellent local control and abscopal responses – this systemic impact on unirradiated metastases is attenuated with alternative radiation-dose regimens.[23] Mechanistically, radiation induced double-stranded DNA breaks accumulate in tumor cells and activate cGAS/STING/IFN signaling, ultimately leading to a potent tumor-specific CD8+ T-cell adaptive immune response.[23-25] A substantial body of preclinical work has identified additional mechanisms which promote radiation driven immunogenicity, including immunogenic cell death and immunogenic modulation.[26-28] Of particular importance is that radiation may enhance PD-L1 expression on both tumor and immune cells via IFN-ɣ-based mechanisms and synergy with anti-PD-1/PD-L1 ICB is evident across several murine models.[29-32]

Given dual cytotoxic and immunomodulatory properties, there is considerable clinical interest in combining SBRT with anti-PD-1/PD-L1 ICB to exploit this biology and evaluate the concept that radiation can convert an irradiated tumor into an in-situ vaccine which primes anti-tumor immune responses both locally and systemically. As such, leaving the irradiated prostate in situ could yield an immunological advantage as compared with surgical extirpation. While clinical experience combining SBRT and ICB is nascent, a recent phase I study of multi-site SBRT and sequential pembrolizumab in advanced metastatic disease provides proof-of-concept. Paired biopsies demonstrated an upregulated IFN-ɣ-associated gene signature in a subset of non-irradiated tumors after SBRT (prior to pembrolizumab) alluding to an intriguing systemic immune-modulating effect of local treatment.[33] While ICB has transformed prognosis for subsets of patients, clinical activity as a monotherapy in prostate cancer has been modest relative to other solid tumors.[34] It is notable that the preponderance of clinical data comes from the metastatic castrate-resistant (mCRPC) population. Post-hoc analyses of mCRPC patients treated with sipuleucel-T or ipilimumab suggest that patients with less advanced disease and lower disease

burden derive the greatest benefit from immune-based approaches.[35-37] This is corroborated by recent evidence that progression to mCRPC is driven by myeloid-derived IL-23 in the immunosuppressive tumor microenvironment.[38] Alternatively, androgen ablation has been shown to promote prostatic infiltration of tumor-specific T-cells and mitigate immune tolerance.[39] Taken together, this suggests that androgen ablation and a hormone-sensitive state may be necessary to optimally respond to immunotherapy. As such, mHSPC may represent an ideal population where a multi-modal combination of anti-PD-L1 ICB and SBRT in the context of androgen ablation (AR targeted therapy and GnRH analogue) could offer substantial clinical benefit.

We hypothesize that the combination of atezolizumab, AR targeted therapy, GnRH analog, and SBRT to the prostate will result in an extension of failure-free survival compared to abiraterone + GnRH analog alone in subjects with mHSPC.

As of November 2021, 24 patients were enrolled to this trial under the treatment schema including the combination of atezolizumab, abiraterone acetate + prednisone, GnRH analog, and SBRT. Of the 24 patients enrolled, 2 patients experienced a Grade 4 colonic perforation. It is the judgment of the sponsor principal investigator that low dose prednisone given with abiraterone combined with atezolizumab in patients with significant diverticular disease in the setting of SBRT could have potentially contributed to these events. Given that safety data exists for the combination of atezolizumab and enzalutamide and enzalutamide has recently been approved in subjects with mHSPC,[9] upon approval of protocol version 4.0, abiraterone acetatewill be replaced with enzalutamide, relevant exclusion criteria will be added and the field of SBRT will be reduced, to mitigate the risk of colonic perforation seen previously.

2. OBJECTIVES

2.1 Primary Objective

To determine if the addition of SBRT and atezolizumab to AR targeted therapy + GnRH analog improves freedom-from-failure (binary) at 2-years relative to the failure-free survival at 2 years in the STAMPEDE trial (70%) for the metastatic cohort.[7] Failure is defined as:

i. Biochemical Failure (see Section 8) **or**:
ii. Radiographic progression defined by PCWG3 **or**
iii. Death due to any cause

2.2 Secondary Objectives

To determine:

- Symptomatic skeletal events (SSEs) defined as symptomatic fracture, surgery or radiation to bone, or spinal cord compression
- Prostate Cancer Specific Survival: defined as time from treatment start to death from prostate cancer; patients who die from other causes will be classified as a competing risk
- Overall Survival: time from start of treatment to death due to any cause; surviving patients will be censored at time of last follow up
- Assess safety and tolerability and measure proportion of adverse events by CTCAE v5.0

2.3 Correlative/Exploratory/Tertiary Objectives

To evaluate potential tissue and blood-based predictors of response to therapy. Correlative outcomes include, but are not limited to:

- **Biopsy Specimens** (Diagnostic baseline prostate biopsy and optional metastatic biopsy, prostate biopsy at time of fiducial placement, and metastatic biopsy upon progression of disease 21 days after discontinuation of treatment). We will evaluate tumor mutation burden (TMB) using genomic profiling assays, gene expression profiles of tumor microenvironment using RNA Sequencing (RNAseq), immunohistochemistry (IHC) analysis of tumor infiltrating lymphocytes, PD-L1 expression. Subjects will have genetic testing according to local site practice.
- **Peripheral Blood Specimens** (at C1D1, C2D1, C4D1, C6D1, and upon progression of disease/End of treatment): we will evaluate changes in T cell phenotype and MDSC populations, TCR richness and diversity, immunophenotypic changes via CyTOF and ctDNA.
- **Fiducial Marker Placement (at C1D14 for first 20 subjects and C3D1 for remaining subjects):** we will compare biopsy results of subjects from both cohorts based on timing of marker placement.

3. SUBJECT SELECTION

3.1 Inclusion Criteria

To be included in this study, subjects should complete all screening procedures and meet all the following criteria:

3.1.1 Willing and able to provide or have a legally authorized representative to provide written informed consent and HIPAA authorization for the release of personal health information. A signed informed consent must be obtained before screening procedures are performed.

NOTE: HIPAA authorization may be either included in the informed consent or obtained separately.

3.1.2 Males 18 years of age and above.

3.1.3 Untreated metastatic (M1a/b/c) hormone-sensitive prostate cancer documented by positive bone scan or metastatic lesion on CT or MRI; untreated is defined as having never had surgery or radiation therapy with the intent to definitively treat the cancer in the prostate.

Note: Subjects who have had prior hormonal therapy (GnRH analog +/- first-generation anti-androgen such a bicalutamide) started up to 3 months prior to signing consent to the trial will be permitted to enroll onto the study if they have demonstrated a decline in PSA. Anti-androgens must be stopped prior to Cycle 1

Note: patients who have started bicalutamide (Casodex) with or without a GnRH analog must stop prior to being registered on trial.

3.1.4 Biopsy-proven adenocarcinoma of the prostate.

3.1.5 Eligible for SBRT per institutional guidelines.

3.1.6 ECOG status of 0 or 1 (Appendix A: Performance Status Criteria).

3.1.7 Normal organ function with acceptable initial laboratory values within 14 days of treatment start:

Absolute Neutrophil Count (ANC)	≥ 1,500 /µl
Absolute Lymphocyte Count (ALC)	≥ 0.5×10^9/L (500/µL)
Albumin	≥ 3.5 g/dL
Hemoglobin	≥ 9 g/dL
Platelet count	≥ 100,000 /µl
Creatinine	within institutional normal limits
Potassium	≥ 3.5 mmol/L (or within institutional normal range)
Bilirubin	≤ 1.5 x ULN (Patients with known Gilbert disease: serum bilirubin ≤3 x ULN)
SGOT (AST), SGPT (ALT), and Alkaline Phosphatase (ALP)	≤2.5 x ULN with the following exceptions: Patients with documented liver metastases: AST and ALT ≤ 5 x ULN; Patients with documented liver or bone metastases: ALP ≤ 5 x ULN
INR	≤1.5 x ULN (unless on anti-coagulation medication such as coumadin in which case elevated INR is permitted)

3.1.8 Subjects must agree to use a medically acceptable method of birth control (e.g., spermicide in conjunction with a barrier such as a condom) or sexual abstinence for the duration of the study, including 150 days after the last dose of study drug. Sperm donation is prohibited during the study and for 150 days after the last dose of study drug. Female partners must use hormonal or barrier contraception unless postmenopausal or abstinent.

3.1.9 Subjects must have adequate tissue available for genomic profiling tests (refer to lab manual for required amount of each correlative test). If subject's pathology is from an outside lab, verbal confirmation from the host lab that 20-35 unstained slides are available is acceptable (fewer slides may be accepted on a case-by-case basis). If cores are available, 5 cores are enough to create 20-35 slides.

3.2 Exclusion Criteria

3.2.1 History of malignancy within 3 years prior to initiation of study treatment, except for malignancies with a negligible risk of metastasis or death (e.g., 5-year OS rate > 90%), such as non-melanoma skin carcinoma and superficial urothelial cancer.

3.2.2 Pathological finding consistent with pure small cell carcinoma of the prostate (no adenocarcinoma in the biopsy specimen).

3.2.3 Known or suspected brain metastasis or active leptomeningeal disease.

3.2.4 Uncontrolled tumor-related pain. Patients requiring pain medication must be on a stable regimen at study entry. Symptomatic lesions (e.g. bone metastases causing nerve impingement) amenable to palliative radiotherapy should be treated prior to enrollment. Patient should be recovered from effects of radiation. There is no required minimum recovery period. Asymptomatic metastatic lesions that would likely cause functional deficits or intractable pain with further growth (e.g., epidural metastasis that is not currently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment).

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

3.2.6 Uncontrolled hypertension (systolic blood pressure ≥160 mmHg or diastolic BP ≥95 mmHg). Subjects with a history of hypertension are allowed provided blood pressure is controlled by anti-hypertensive treatment.

3.2.7 Positive HIV test at screening.

3.2.8 Active hepatitis B virus (HBV) infection (chronic or acute), defined as having a positive hepatitis B surface antigen (HBsAg) test and/or HBV PCR at screening. Patients currently treated with anti-viral therapy for HBV. Subjects with a past or resolved HBV infection, defined as having a negative HBsAg and HBV PCR test and a positive total hepatitis B core antibody (HBcAb) test at screening, are eligible for the study.

3.2.9 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 subjects who have a positive HCV antibody test.

3.2.10 History of adrenal dysfunction.

3.2.11 Uncontrolled or symptomatic hypercalcemia (ionized calcium > 1.5 mmol/L, calcium > 12 mg/dL or corrected serum calcium > ULN).

3.2.12 Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis, with the following exceptions:

- Subjects with a history of autoimmune-related hypothyroidism who are on thyroid replacement hormone
- Subjects with controlled Type 1 diabetes mellitus who are on an insulin regimen
- Subjects with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., subjects with psoriatic arthritis are excluded) are allowed provided all the 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

3.2.13 Past medical history of bowel obstruction.

3.2.14 Past medical history of colonic perforation.

3.2.15 History of prior seizure activity or use of current medications that increase the plasma concentration of enzalutamide.

3.2.16 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.

3.2.17 Active tuberculosis.

3.2.18 Significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac disease, myocardial infarction, cerebrovascular accident, unstable arrhythmia or unstable angina) within 6 months prior to initiation of study treatment.

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

3.2.20 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.

3.2.21 Prior allogeneic stem cell or solid organ transplantation.

3.2.22 Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during atezolizumab treatment or within 5 months after the final dose of atezolizumab.

3.2.23 Treatment with investigational therapy within 28 days prior to initiation of study treatment.

3.2.24 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.

3.2.25 Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti-CTLA-4, anti-PD-1, and anti-PD-L1 therapeutic antibodies.

3.2.26 Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2 [IL-2]) within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to initiation of study treatment.

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

- Subjects 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 after Sponsor Principal Investigator approval has been obtained.
- Subjects 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.

3.2.28 History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins.

3.2.29 Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab formulation.

3.2.30 Known allergy or hypersensitivity to any component of the enzalutamide formulation.

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

4. ENROLLMENT PLAN

4.1 Enrollment Plan

4.1.1 *Anticipated Enrollment*
This study is anticipated to enroll 44 subjects.

4.1.2 *Recruitment*
Potential research subjects will be identified by a member of the subject's treatment team, the protocol investigator, or research team at participating centers from Medical Oncology, Radiation Oncology and Urology offices. Investigators will screen the subject's medical records for suitable research study subjects and discuss the study and their potential for enrolling in the research study.
Subjects may be provided access to a video link if interested in participating in the trial; https://progress.standuptocancer.org/catalyst?team=prostate-cancer. The video can assist subjects in understanding the SAABR trial.

4.2 Eligibility Confirmation

Confirmation of eligibility will be completed centrally by the PCCTC prior to treatment start. A record of subjects who fail to meet eligibility criteria (i.e., screen failures) will be maintained. **A complete, signed informed consent and HIPAA authorization are required as part of eligibility confirmation.** All subjects must sign an IRB-approved informed consent prior to starting any protocol-specific procedures; however, evaluations performed as part of routine care prior to informed consent can be used for screening and eligibility confirmation.

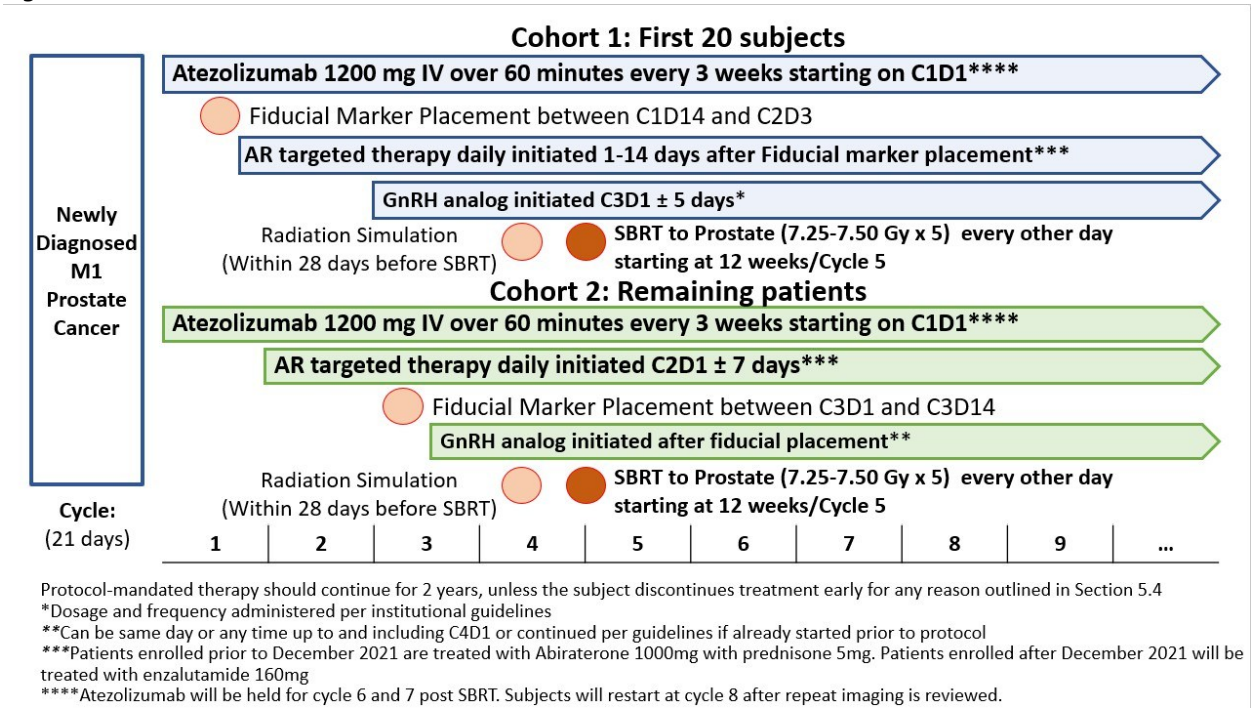
5. TREATMENT PLAN

Continue treatment until disease progression, unacceptable toxicity, or any criteria in **Section 5.4** for protocol mandated period of 2 years after which atezolizumab will be stopped; continuation

of AR targeted therapy and GnRH analog is up to the discretion of the treating physician per local standard of care.

All subjects will follow the treatment schema described in Figure 1.

Figure 1. Treatment Schema



Protocol-mandated therapy should continue for 2 years, unless the subject discontinues treatment early for any reason outlined in Section 5.4
*Dosage and frequency administered per institutional guidelines
**Can be same day or any time up to and including C4D1 or continued per guidelines if already started prior to protocol
***Patients enrolled prior to December 2021 are treated with Abiraterone 1000mg with prednisone 5mg. Patients enrolled after December 2021 will be treated with enzalutamide 160mg
****Atezolizumab will be held for cycle 6 and 7 post SBRT. Subjects will restart at cycle 8 after repeat imaging is reviewed.

Note: *Subjects may start GnRHanalog up to 3 months prior to signing consent for treatmentand will be placed in Cohort 2*

Atezolizumab will be administered by intravenous (IV) infusion at a fixed dose of 1200 mg IV over 60 minutes every 3 weeks along with AR targeted therapy, GnRH analog (dosage and frequency should follow institutional guidelines), and SBRT (7.25-7.5 Gy x 5 fractions to prostate and seminal vesicles every other day starting at C5D1 ±5 days) until unacceptable toxicity, protocol defined progression, or two years of treatment. The fiducial marker will be placed on the first 20 subjects (cohort 1) taking atezolizumab only between C1D14-C2D3, and the remaining subjects (cohort 2) taking both AR targeted therapy and atezolizumab, will received the fiducial marker between C3D1-C3D14. We will compare the biopsy results from these 2 groups of subjects for correlative analyses as stated in the exploratory objectives (Section 2.3) and analysis plan (Section 10). Atezolizumab will be continued for a maximum of two years. Continuation of AR targeted therapy and GnRH analog beyond two years is at the discretion of the treating physician per local standard of care. For patients with high risk localized disease treated in the STAMPEDE protocol, hormone therapy with AR targeted therapy was continued for a minimum of two years, hence the treatment length recommendation in this protocol. Since this population of subjects have metastatic disease, the investigators may choose to continue AR targeted therapy until

progression based on data from LATTITUDE and STAMPEDE. Atezolizumab will be continued for 2 years to optimize potential treatment benefit in the setting of SBRT.

Currently, no published safety data are available with the combination of atezolizumab and abiraterone. Based on the different mechanism of action for each product, the overlapping risks of abiraterone, prednisone and atezolizumab were thought to be minimal and were not expected to significantly increase the incidence of adverse events seen in monotherapy studies. 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 subjects treated with atezolizumab monotherapy and in combination therapy (see atezolizumab Investigator's Brochure for detailed safety results).

This trial initially elected to use abiraterone and prednisone as the AR directed therapy of choice since AR antagonists such as apalutamide and enzalutamide had not yet been approved for use in mHSPC. During the conduct of the trial, 2 out of 24 patients treated on study (both of whom had a history of significant diverticulosis) had an unexpected SAE of colonic perforation occurring within 3 months of receiving SBRT. Upon further review it was felt that the combination of abiraterone and prednisone with atezolizumab in the setting of SBRT in patients with diverticulosis could have potentially contributed to the colonic perforation in these patients with a known history of diverticulosis through the following inter-related mechanisms: 1) increased risk of GI toxicity/constipation with abiraterone in the setting of diverticulosis, 2) a mild inflammatory response to atezolizumab further triggered by SBRT, 3) thinning of the colonic wall along with masking of mild GI inflammatory symptoms with the use of prednisone. As such, we have elected to remove abiraterone and prednisone from the study intervention and proceed with enzalutamide in its place since enzalutamide is not given with prednisone and is now approved for use in mHSPC (ENZAMET, ARCHES). In addition, the combination of enzalutamide and atezolizumab has been extensively studied in mCRPC and the safety profile has been well-established from the IMBassador250 trial. As a further precautionary measure, we plan toreduce the field of SBRT and exclude the seminal vesicles to further decrease any associated risk due to scattered radiation to the sigmoid colon and will exclude patients with a clinically significant history of sigmoid diverticulosis from study treatment going forward. Notably, patients already on trial without a history of diverticulosis and > 3 months past SBRT have been given the option to continue treatment with abiraterone/prednisone with or without atezolizumab.

Upon approval of protocol version 4.0, abiraterone acetate with prednisone will be replaced with enzalutamide. Subjects will continue on treatment until disease progression, unacceptable toxicity, or any criteria in **Section 5.4** for protocol mandated period of 2 years after which atezolizumab will be stopped; continuation of enzalutamide and GnRH analog is up to the discretion of the treating physician per local standard of care. Enrollment will continue as planned with Cohort 1 enrolling up to 20 patients and the remainder of patients enrolling to cohort 2. Subjects on prior hormonal therapy up to 3 months prior to signing consent are eligible to enroll.

The timing of all treatments in cohorts will remain upon approval of protocol version 4.0. In addition to enzalutamide replacing abiraterone acetate, the following changes have been made to atezolizumab treatment and SBRT:

- Atezolizumab will be administered by intravenous (IV) infusion at a fixed dose of 1200 mg IV over 60 minutes every 3 weeks. Subjects will hold atezolizumab post SBRT for Cycles 6 and 7. Subjects will continue on atezolizumab at Cycle 8 after reimaging with no evidence of colonic edema or inflammation.
- Subjects will receive a reduced volume of SBRT to decrease scatter radiation to the sigmoid colon. SBRT will be given to the prostate (7.25-7.50 Gy X 5) every other day starting at Cycle 5. The use of rectal spacers is prohibited on trial.

The decision to replace abiraterone with enzalutamide is supported by safety data available for the combination of atezolizumab and enzalutamide.[40] Measures will be taken to ensure the safety of subjects participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of subjects. There will be continuous toxicity monitoring with clearly defined early stopping rules (see statistical section). Assessments and procedures detailed in Section 5.1 will occur during the study. A schedule of assessments is provided in Appendix B.

5.1 Study Procedures

Screening *(all elements of which must be obtained/recorded within 30 days prior to treatment start. Some eligibility assessments (e.g imaging and lab assessments) may have different windows for screening.):*

5.1.1 Informed consent and research/HIPAA authorization

Before initiating any protocol-specific screening activities, the scope of the study should be explained to each subject. Subjects should be consented in accordance with section 12.2 Informed Consent, including completion of a research/HIPAA authorization.

5.1.2 Inclusion/exclusion criteria

During the screening period, subject eligibility will be determined according to the inclusion and exclusion criteria (Sections 3.1 Inclusion Criteria & 3.2 Exclusion Criteria).

5.1.3 Demographics and medical history

Demographics and medical history collected will include:

- Date of birth (or age if date of birth is not allowed to be collected by local regulations)
- Significant past and ongoing conditions
- Details of prior prostate cancer biopsies and surgeries
- Comorbidities

5.1.4 Histologic confirmation of disease

5.1.5 Concomitant medications

Concomitant medications are permitted while on study if the medication is not expected to interfere with the evaluation of safety or efficacy and does otherwise restricted or prohibited (see Appendix C and D for a listing of medications with the potential for drug interactions).

Because of the potential for drug-drug interaction, the concurrent use of all other drugs, over-the-counter medications, and alternative therapies must be documented on the eCRFfrom the screening through 30 days after last treatment.

All herbal supplements are discouraged due to unknown interaction with study drugs and radiation.

5.1.6 Vital signs and weight

Vitals will include temperature, blood pressure, and pulse. Weight will also be collected as described in Appendix B.

5.1.7 Subject Status

Performance status will be assessed using the ECOG scale (Appendix A)

5.1.8 Physical Examination

A complete physical examination will be performed at screening. A symptom-directed physical exam should be performed at subsequent visits as noted in Appendix B.

5.1.9 Laboratory Tests

Laboratory tests will be performed by treating institutionand will include. Some labs may be required to be drawn 14 days prior to treatment start. Please refer to inclusion 3.1.7):

- CBC with differential
- Comprehensive Metabolic Panel
- PSA
- Testosterone
- Coagulation: PTT/PT and INR
- Amylase/Lipase
- TSH and Free T4
- C-Reactive Protein
- Hepatitis B (HBsAg and HBV PCR) and Hepatitis C screening per center standards
- HIV Serology

5.1.10 ECG

A screening ECG will be performed. All ECGs should be 12-lead ECGs. Additional unscheduled 12-lead ECGs may be conducted when necessary at the investigator's discretion.

5.1.11 Imaging

Imaging must include RECIST documentation from a study radiologist for soft tissue measurements identified on CT scans. Bone scans will be reviewed by the study radiologist and sites of disease will be documented per PWG3 .

5.1.11.1 *Dedicated MRI of the Prostate within 90 days prior to treatment start*

5.1.11.2 *CT Chest/Abdomen/Pelvis (or CT Chest and MR Abdomen/Pelvis) will be completed at screening within 30 days prior to treatment start, 8 weeks from C1D1 and then every 8 weeks from the date of the subject's previous scan (+/- 4 weeks) for 1st year and then every 12 weeks (+/- 4 weeks) during the 2nd year. CT chest/abdomen/pelvis, preferably with contrast or MRI abdomen/pelvis with CT chest. The same modality should be used throughout the course of the study.*

5.1.11.3 *Technitium 99 Whole Body Bone Scan will be completed at screening within 90 days prior to treatment start, 8 weeks from C1D1 and then every 8 weeks from the date of the subject's previous scan (+/- 4 weeks) for 1st year and then every 12 weeks (+/- 4 weeks) during the 2nd year.*

5.1.12 Up-front biopsy of prostate is mandatory, biopsy of metastatic site is optional. If adequate material from a previous prostate biopsy is available, the archival tissue may be sent in lieu of a new prostate biopsy.

5.1.13 Baseline blood draw for correlatives drawn C1D1 prior to treatment start.

5.1.13.1 Blood will be collected for T cell and MDSC flow cytometry, TCR sequencing, CyTOF and ctDNA analysis. Collection, processing and shipment instructions can be found in the laboratory manual.

5.1.13.2 **Columbia University Medical Center (CUMC) only**: Blood sample will be collected as a normal control for the institutional genomic profiling. Collection, processing and shipment instructions can be found in the laboratory manual.

On-Treatment: Telemedicine and local assessments are able to be completed as necessary. Physical exams will be waived for telemedicine visits and not require a deviation to be completed. Correlative blood draws cannot be waived or done locally and will need to be arranged to be completed onsite.

5.1.14 Atezolizumab: will be administered on C1D1 and then every 21 days (±3 days) *from the date of the subject's previous atezolizumab administration*);

5.1.15 Fiducial marker placement and on-treatment prostate biopsy:

5.1.15.1 Cohort 1: must occur between C1D14 and C2D3 and include a visually targeted, MR guided, multi-core biopsy of the dominant lesion.

5.1.15.2 Cohort 2: must occur between C3D1 and C3D14 and include a visually targeted, MR guided, multi-core biopsy of the dominant lesion.

Fiducial markers will be placed on all subjects enrolled in the study since all subjects will receive radiation.

5.1.16 Abiraterone: 1000mg po QD and prednisone 5mg po QD (Subjects enrolled after protocol version 4.0 will not receive abiraterone and prednisone):

5.1.16.1 Cohort 1: will be started between 1-14 days after fiducial placement and continued per protocol guidelines.

5.1.16.2 Cohort 2: will be started on Cycle 2 Day 1 (+/- 7 days) and continued per protocol guidelines.

5.1.17 Enzalutamide: 160mg po QD (Subjects enrolled upon approval of protocol version 4.0)

5.1.17.1 Cohort 1: will be started between 1-14 days after fiducial placement and continued per protocol guidelines.

5.1.17.2 Cohort 2: will be started on Cycle 2 Day 1 (+/- 7 days) and continued per protocol guidelines.

5.1.18 GnRH analog: will be initiated C3D1 ±5 days (dose and frequency should follow institutional guidelines). Patients already on GnRH analog upon study enrollment will continue throughout the study period.

5.1.19 Radiation Simulation: should occur within 28 days of planned start of SBRT.

5.1.20 Stereotactic Body Radiotherapy (SBRT) to the prostate/seminal vesicles: will start on C5D1 ±5 days; treatment should be completed *within 21 days. Upon approval of protocol version 4.0, subjects will not receive SBRT to the seminal vesicles in order to reduce scattered radiation to the sigmoid colon.*

5.1.21 Correlative Blood Draws: Blood for T cell and MDSC flow cytometry, TCR sequencing, CyTOF and ctDNA analysis will be collected on C2D1 (±3 days), C4D1 (±3 days), C6D1 (±3 days), and upon progression of disease (POD) at the End of Treatment visit. Baseline blood draw for correlatives should be drawn prior to treatment start on C1D1 (see 5.1.13.1).

5.1.22 Laboratory Tests: CBC with differential: white blood cells count (WBC), red blood cell count (RBC), hemoglobin (HGB), hematocrit (HCT), platelet count (UNVPLT), neutrophils (NEUTP), lymphocytes (LYMP), monocytes (MONP), eosinophils (EOSP), basophils (BASOP)); Comprehensive Metabolic Panel: (glucose (GLU), calcium (CA), albumin (ALB), total protein (TP), sodium (NA), potassium (K), bicarbonate (CO2), chloride (CL), blood urea nitrogen (BUN), creatinine (CREAT), alkaline phosphatase (ALK), alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin (TBILI), magnesium (MG); PSA; serum testosterone/dihydrotesterone (TEST); amylase; lipase; TSH; Free T4; C-Reactive Protein (CRP); Hepatitis B and C, and HIV Serology. Serum testosterone will be collected on Day 1 of each cycle through Cycle 6. Hepatitis B and Hepatitis C, HIV Serology, and CRP are required at screening only.

5.1.22.1 AST, ALT and total bilirubin (LFTs) should be monitored on Day 1 or Day -1 of each treatment cycle. LFTs should also be drawn every 2 weeks (+/- 1 week or at investigator's discretion to correlate with treatment cycles) for the first 3 months after starting abiraterone and prednisone. Subjects starting enzalutamide instead of abiraterone and prednisone only require LFTs to be monitored on Day 1 or Day -1 of each treatment cycle. Labs may be drawn at an outside facility.

(NOTE: LFTS must be resulted prior to treatment for Cycles 1-5 and may be drawn the day prior to treatment)

5.1.23 PCWG3 and RECIST tumor measurements to be repeated with each imaging timepoint.

5.1.24 Adverse event evaluation should occur from the time of treatment start until the End of Treatment visit (within 30 days of last dose). See section 5.3 for additional information.

5.2 Correlative/Special Studies

5.2.1 ***Biopsy Correlatives (baseline prostate and optional metastatic biopsy, on-treatment prostate biopsy (at time of fiducial placement), and metastatic biopsy at progression) including, but not limited to:***

- *MSK-IMPACT next-generation sequencing for TMB and mutation profiling. Subjects will have genetic profiling according to local site practice.* The MSK-IMPACT assay is a custom targeted sequencing platform, utilizing solution phase exon capture and sequencing of DNA from matched tumor and germline tissue to detect somatic alterations (point mutations, small insertions and deletions, and microsatellite instability) in all protein-coding exons of cancer-associated genes from tumor specimens.[41] The assay is performed within a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory. Local realignment and quality score recalibration are performed using Genome Analysis Toolkit (GATK) according to GATK best practices. Samples are subjected to a series of computational quality control steps to ensure genomic concordance between tumor and normal specimens from the same specimen, detect the presence of tumor DNA in the normal sample, and monitor contamination involving DNA from different samples. Paired-sample variant calling is performed on tumor samples and their respective matched normal to identify point mutations/single nucleotide variants and small insertions/deletions (indels) using MuTect (version 1.1.4) and SomaticIndelDetector (a tool in GATKv.2.3.9), respectively. The MSK-IMPACT assay will be performed in the CLIA-certified Molecular Diagnostics Service laboratory at MSKCC. If the assay is run clinically (for MSKCC subjects only), a pathology report including the somatic mutations of the sequenced tumor will be returned to the treating physician for further review with his/her patient. The clinical molecular profiling data, obtained in the context of this protocol, will be entered into a HIPAA-compliant, de-identified, access-controlled database, known as the cBioPortal. This data will be stored in the cBioPortal for future, unspecified use by Memorial Sloan Kettering.
- *Gene expression profiles (GEP) of immune tumor microenvironment (TME)***:** using NanoString RNAseq, we will evaluate IFN-γ-related genes (IFNG, IDO1, CXCL9/10, HLA-DRA, STAT1), which predict response to ICI, as well as CD8+ effector T cells (CD8, PRF1, GZMB), and Th1 CD4+ (IFNG, T-bet, FUT7, CCL3, CXCR5). Comparisons of the percentage change in lymphocyte subsets and fold-change in genes-of-interest (t-test, p-value, false discovery rate) will be performed.
- *IHC of tumor infiltrating lymphocytes and PD-L1 expression*: Biopsy samples will be assessed by standard IHC for CD3, CD4, CD8, and Foxp3 to compare the changes in ratio of effector T cells to regulatory T cells. IHC for PD-L1 will also be assessed analyzed on Ventana instrumentation (per in-house validation), which shows near 100% concordance. Tumor Proportion Score (TPS) will be reported.
- Two additional tissue cores will be collected during each fresh biopsy, snap-frozen and used for gene expression profiling.

5.2.2 ***Peripheral blood correlatives*** *Multicolor Flow Cytometry, which may include, but is not limited to, the below panels will be performed:*

- *T cell exhaustion/activation:* Live-Dead, CD3, CD4, CD8, FoxP3, Ki-67, ICOS, PD-1, LAG-3, TIM-3, CTLA-4; ~3 stains per sample: 2 Ab-specific duplicate stains, 1 isotype control stain.
- *MDSC panel:* Live-Dead, CD14, HLA-DR, and lineage cocktail (CD3, CD16, CD19, CD20, CD56).

- *TCR sequencing to evaluate diversity and clonal selection*
- *Mass cytometry (CyTOF) for further immunophenotyping*
- *Circulating tumor DNA (ctDNA)*

5.3 Follow-up

Subjects who discontinue study treatment for reasons other than progression will be followed every 6 months (+/- 4 weeks) until a documented progression event (i.e., PSA, radiographic, or clinical progression). After a documented progression event (whether on treatment or during follow up), subjects will continue to be followed every 6 months (+/- 4 weeks) for overall survival via chart review and/or telephone call. Subjects will be removed from follow up and come off study should one of the following occur: lost to follow-up, withdrawal of consent (documented in the medical record), or study termination. Subjects withdrawn from the study because of AEs will be followed until the adverse event has either resolved or stabilized. Reasons for premature withdrawal should be determined and noted. Subjects may be followed more frequently to monitor for treatment related side effects by discretion of the treating investigator.

Subjects who progress will have correlative blood drawn at the End of Treatment visit.

Subjects who progress will have biopsy of a selectedprogressive lesion prior to initiation of new therapy when feasible.

5.4 Removing Subjects from Treatment

In the absence of treatment delays because of adverse events, protocol-mandated treatment will continue through Cycle 35 (Day 735) of the protocol (with continuation of AR targeted therapy/GnRH analog beyond 2 years per treating physician) or until one of the following criteria applies:

- Withdrawal by subject: subject decides to withdraw from the study
- Holding of either drug for a continuous time >12 weeks
- Subject failure to follow study requirements
- Protocol-defined progressive disease and/or no clinical benefit as determined by the treating physician per PCWG3 guidelines
- Protocol deviation:
  - intercurrent illness that prevents further administration of treatment

- Adverse event: unacceptable adverse event(s) that may or may not be directly related to treatment but that, in the judgment of the treating physician, makes it dangerous for the subject to be retreated
- Physician decision: general or specific changes in the subject's condition that render the subject unacceptable for further treatment in the judgment of the investigator
- Study termination by sponsor

Subjects who show signs of progression may continue treatment on study past initial progression if, as determined by the Investigator, they could still clinically benefit from continued study, as outlined in the PCWG3 recommendations.[42] In this setting, palliative RT is allowed.

If a subject voluntarily withdraws from the study, attempts should be made to contact the subject to determine and record the reason(s) for discontinuation. All procedures and evaluations required by the Final Visit should be completed in the event of early withdrawal, regardless of reason. All subjects who discontinue the study secondary to an adverse event must be followed until resolution or stabilization of the adverse event.

5.4.1 Rationale for atezolizumab treatment beyond initial radiographic progression

In studies of immunotherapeutic agents, complete response, partial response, 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.[43] In study PCD4989g, evidence of tumor growth followed by a response was observed in several tumor types. In addition, in some responding subjects with radiographic evidence of progression, biopsies of new lesions or areas of new growth in existing lesions revealed ICs and no viable cancer cells. Because of the potential for a response after pseudoprogression, this study will allow subjects to continue treatment after apparent protocol-defined progression, provided the benefit-risk ratio is judged to be favorable by the investigator and the subject agrees to continue treatment.Subjects who pseudo progress will be counted as having failed for the primary endpoint. Subjects should be discontinued for unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status.

6. THERAPEUTIC MODALITIES

6.1 Atezolizumab

The atezolizumab 1200 mg drug product will be supplied in a single-use, 20-mL USP/Ph. Eur. Type 1 glass vial as a colorless to slightly yellow, sterile, preservative-free clear liquid solution intended for IV administration. The vial is designed to deliver 20 mL (1200 mg) of atezolizumab solution but may contain more than the stated volume to enable the delivery of the entire 20-mL volume.

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

6.1.1 Cautionary therapy for atezolizumab-treated subjects

Corticosteroids and Tumor Necrosis Factor-α Inhibitors

Systemic corticosteroids and TNF-α inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations in which systemic corticosteroids or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids and TNF-α 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. Physiologic prednisone of 10 mg daily is allowed on study. Doses higher than this used to treat adverse events are allowed but must be reported to the Sponsor Principal Investigator.

Herbal therapies

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

6.1.2 Prohibited therapy

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

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority–approved or experimental, is prohibited for various time periods prior to starting study treatment, depending on the agent (see Section 4.1.2), and during study treatment until disease progression is documented and the subject has discontinued study treatment.

  Note: Focal palliative radiation therapy (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.

- 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.

6.1.3 Prohibited food

Consumption of grapefruit juice, a potent CYP3A4 enzyme inhibitor, is prohibited during the study and for 30 days after the last dose of study treatment.

Permitted Therapy

- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)
- Vaccinations (such as. influenza, SARS-CoV-2)

  Live, attenuated vaccines are not permitted (see Section 4.4.3).
- Megestrol acetate administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Corticosteroids administered for COPD or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency

6.2 Abiraterone

Upon approval of protocol version 4.0, newly enrolled subjects will no longer receive abiraterone).

6.2.1 Dosage and administration

The recommended dose of abiraterone acetate is 1000 mg administered orally once daily in combination with prednisone 5 mg administered orally once daily.[44] Abiraterone must be taken on an empty stomach. No food should be consumed for at least two hours before the dose of abiraterone is taken and for at least one hour after the dose of abiraterone is taken. The tablets should be swallowed whole with water.

6.2.2 Supply, storage, and handling

Abiraterone 250 mg tablets are white to off-white, oval tablets debossed with AA250 on one side. Abiraterone 250 mg tablets are available in high-density polyethylene bottles of 120 tablets.

NDC Number 57894-150-12

<u>Storage and Handling</u>

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

Based on its mechanism of action, abiraterone may harm a developing fetus. Therefore, women who are pregnant or women who may be pregnant should not handle abiraterone without protection, e.g., gloves.

6.2.3 Potential for drug-drug interactions

<u>Effects of Abiraterone on Drug Metabolizing Enzymes</u>

Abiraterone is an inhibitor of the hepatic drug-metabolizing enzyme CYP2D6. In a CYP2D6 drug-drug interaction trial, the C_{max} and AUC of dextromethorphan (CYP2D6 substrate) were increased 2.8- and 2.9-fold, respectively, when dextromethorphan was given with abiraterone acetate 1000 mg daily and prednisone 5 mg once daily. Avoid co-administration of abiraterone with substrates of CYP2D6 with a narrow therapeutic index (e.g., thioridazine). If alternative treatments cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate drug.

Drugs that Inhibit or Induce CYP3A4 Enzymes

Based on in vitro data, abiraterone is a substrate of CYP3A4. The effects of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole) or inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital) on the pharmacokinetics of abiraterone have not been evaluated, in vivo. Avoid or use with caution, strong inhibitors and inducers of CYP3A4 during Abiraterone treatment.

See Appendix C for a full listing of medications with the potential for drug interactions.

6.2.4 Dose adjustments

Dose adjustments for abiraterone may be made according to the prescribing information (see abiraterone Package Insert). Any dose changes and the reasons need to be documented in the subject's medical record and in the eCRF. If there is a substantial abiraterone dose delay, particularly if an entire dosing period is skipped, then if possible subjects should still come to the clinic to receive tumor assessments at the usual time despite the dosing delay. When abiraterone held, prednisone should continue when the toxicity has resolved or improved to an acceptable level.

6.3 Enzalutamide

Upon approval of protocol version 4, newly enrolled subjects will receive enzalutamide.

6.3.1 : Dosage and administration

The recommended dose of enzalutamide (XTANDI) is 160 mg (two 80mg tablets or four 40mg tablets) administered orally once daily. Enzalutamide can be taken with or without food. The tablets should be swallowed whole with water.

6.3.2 : Supply, storage and handling

Enzalutamide (XTANDI) 40mg tablets are supplied as yellow, round, film-coated tablets imprinted with E 40. Tablets come in bottles of 120 tablets with child resistant closures. Tablets should be stored at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

6.3.3 : Potential for drug-drug interactions

Drugs that Inhibit CYP2C8

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

should be avoided if possible. If co-administration of XTANDI with a strong CYP2C8 inhibitor cannot be avoided, reduce the dose of XTANDI.

Drugs that Induce CYP3A4
Co-administration of rifampin (strong CYP3A4 inducer and moderate CYP2C8 inducer) decreased the composite AUC of enzalutamide plus N-desmethyl enzalutamide by 37%. Co-administration of strong CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine) with XTANDI should be avoided if possible. St John's wort may decrease enzalutamide exposure and should be avoided. If co-administration of a strong CYP3A4 inducer with XTANDI cannot be avoided, increase the dose of XTANDI.

See Appendix D for interactions with Enzalutamide

Effect of Enzalutamide on Drug Metabolizing Enzymes
Enzalutamide is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer in humans. At steady-state, XTANDI reduced the plasma exposure to midazolam (CYP3A4 substrate), warfarin (CYP2C9 substrate), and omeprazole (CYP2C19 substrate). Concomitant use of XTANDI with narrow therapeutic index drugs that are metabolized by CYP3A4 (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus and tacrolimus), CYP2C9 (e.g., phenytoin, warfarin) and CYP2C19 (e.g., S-mephenytoin, clopidogrel) should be avoided, as enzalutamide may decrease their exposure. If co-administration with warfarin cannot be avoided, conduct additional INR monitoring.

6.3.4 : Dose adjustments

Dose adjustments for enzalutamide may be made according to the prescribing information (see enzalutamide Package Insert). Any dose changes and the reasons need to be documented in the subject's medical record and in the eCRF. If there is a substantial enzalutamide dose delay, particularly if an entire dosing period is skipped, then if possible subjects should still come to the clinic to receive tumor assessments at the usual time despite the dosing delay. Continue enzalutamide when the toxicity has resolved or improved to an acceptable level.

6.4 SBRT

Intensity-modulated, image-guided, ultra-hypofractionated external beam radiotherapy (7.25-7.5 Gy x 5 to prostate and seminal vesicles QOD) will begin around 12 weeks (at Cycle 5 Day 1 (+/-5 days). Upon approval of protocol version 4.0, SBRT will only be given to the prostate and no longer include the seminal vesicles. Reducing the radiation volume is an attempt to decrease scattered radiation to the sigmoid colon.
Image guided, intensity-modulated, ultra-fractionated radiation therapy is considered a reimbursable expense by Medicare.

6.4.1 Prior to Simulation

- Prior to simulation, subjects will be referred for fiducial marker placement.
- Subjects should have fiducial markers at least 4 days prior to simulation.

6.4.2 Simulation

- Subjects will perform a bowel preparation per institutional guidelines.
- Subjects will be supine and positioned in an appropriate immobilization device.
- A Foley catheter can be placed for simulation only.
- A rectal catheter canbe placedfor simulation only.
- CT images will be obtained as per existing department protocols and sent to the treatment planning system
- If available, MR images will be obtained as per existing department protocols, they will be sent to the treatment planning systemas well.
- Subjects should have a comfortably and reproducibly full bladder; although the needfor full bladder is up to the treating radiation oncologist.

6.4.3 Treatment Planning

- CTV1 should include the prostate any areas at risk of extra-capsular extension; no portion of the seminal vesicles should be electively covered.
- PTV1 should include a 0.3-0.5 cmexpansion on CTV1in all directions, savefor posterior; the posterior expansion will be 0.3 cm.f
- For PTV1, the D95% should be ≥90% of the prescribed doseof 7.25-7.5 Gy per fraction.

6.4.4 Contouring of Normal Tissue Structures

Should be performed per institutional standards.
Potential planning objectives and constraints are below, but can defer to home institutions preferences

Prostate 750x5 = 3750cGy Prostate ONLY - NO Nodes	**Target Criteria**			
	PTV Mean Dose = 101-103%			
	PTV Max = 40.12Gy (41.25Gy)			
	PTV $D_{95\%}$ = 35Gy (acceptable) - 37.5Gy (ideal)			
	PTV Min = 35Gy			
	CTV $D_{95\%}$ = 37.5Gy			
	Normal Tissue Criteria			
	Structures	**Todal Dose* or Volume ≤**	**To:**	**Comments**
	Rectum (entire rectum, not just wall)	38.6Gy	Max Point Dose	
		NA	D_{1cc}	
		12.2Gy (15.4Gy)	Mean Dose	
		<25%	V_{24Gy}	
		8%	NTCP	
		8cc	$V_{30.15Gy}$	
		52%	V_{10Gy}	Guideline
	Bladder (entire bladder, not just wall)	39.4Gy	Max Point Dose	
		33.8Gy	$D_{10\%}$	
		18.8Gy	$D_{50\%}$	
	Femoral Heads	31Gy	Max Point Dose	
		20.3Gy	D_{10cc}	
	Skin	30.4Gy	Max Point Dose	
	Penile Bulb	37.5Gy	Max Point Dose	
		20.3Gy	D_{3cc}	
	Large Bowel	29Gy	Max Point Dose	
	Small Bowel	25Gy	Max Point Dose	
	Bladder Trigone	38.6Gy	Max Point Dose	If contoured
	Urethra	39.4Gy	Max Point Dose	
		NA	D_{1cc}	

- Beam arrangements, optimization structures and optimizationparameters will be defined at the discretion of the treatment planner using routine departmental procedures.
- The treatment plan willbe approved and reviewed by the attending physician.
- The treatment plan will go through quality assurance procedures per departmental guidelines.

6.4.5 Treatment Delivery

- Subjects should be treated no more frequently than every other day, excluding holidays and weekends; no more than 2 fractions per week should be delivered. Treatment must be completed within 21 days of first fraction. If the participant must miss one or two scheduled treatments due to unexpected events, theywill be made up and this will not be considered a deviation/violation per protocol.
- Subjects should use an enema three hours prior to each radiation fraction to ensure an empty rectum per institutional guidelines.
- Intra-fraction motion management should be utilized per treating institutionprotocol.
- Rectal spacers are prohibited on trial

6.5 GnRH analog

Any GnRH analog that is commercially available, injectable, and long-acting analog of the native LHRH peptide and is administered to subjects via intramuscular injection. For this study, any GnRH analog can be used and the manufacturer's instructions for dose and frequency should be followed.

6.6 Dose Modifications

There will be no dose modifications for atezolizumab in this study. However, atezolizumab treatment may be temporarily suspended in subjects experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered to the equivalent of $\leq$ 10 mg/day oral prednisone before atezolizumab can be resumed. If atezolizumab or abiraterone or enzalutamide is withheld for $>$ 12 weeks after event onset, the subject will be discontinued from the drug that had been held. However, atezolizumab may be withheld for $>$ 12 weeks to allow for subjects to taper off corticosteroids prior to resuming treatment and can be resumed after being withheld for $>$ 12 weeks if the Sponsor Principal Investigator agrees that the subject is likely to derive clinical benefit. If only one drug is held due to toxicity and is discontinued, the other drug may continue as monotherapy. If unknown attribution for toxicity, both drugs should be held. Atezolizumab or abiraterone or enzalutamide treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). For immune-related AEs that the Sponsor Principal Investigator believes could be reasonably exacerbated by radiation (e.g., immune-related colitis), SBRT will be delayed until resolution to Grade 1.

6.6.1 Management Guidelines

Atezolizumab and/or abiraterone or enzalutamide may be managed independently according to their respective risk profile and be temporarily suspended in subjects experiencing toxicity considered to be related to the respective study drug. Risks associated with atezolizumab and abiraterone and enzalutamide are described in the investigator brochure and package insert, respectively. If corticosteroids are initiated for treatment of the toxicity, they must be tapered to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

Guidelines for management of subjects who experience specific adverse events are provided in the following tables:

Table 1. Management Guidelines for Anaphylaxis

Event	Action to Be Taken
Anaphylaxis	• Discontinue atezolizumab • Continue abiraterone or enzalutamide after symptoms have resolved to baseline.

Anaphylaxis Precautions

EQUIPMENT NEEDED

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for intravenous, intramuscular, and endotracheal administration in accordance with institutional guidelines
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study treatment infusion, the following procedures should be performed:

1. Stop the study treatment infusion.
2. Call for additional medical assistance.
3. Maintain an adequate airway.
4. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring, if possible.
5. Administer antihistamines, epinephrine, or other medications as required by participant status and as directed by the physician in charge.
6. Continue to observe the participant and document observations.
7. Draw serum/plasma samples for immunogenicity testing.
8. Ask participant to return for washout immunogenicity sample if appropriate.

Table 2. Management Guidelines for Infusion-Related Reactions (IRRs) and Cytokine-Release Syndrome

No premedication is indicated for the administration of Cycle 1 of atezolizumab. However, patients who experience an IRR with Cycle 1 of atezolizumab may receive premedication with antihistamines or antipyretics/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.[45] . 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,[46,47] 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. For subsequent cycles, IRRs should be managed according to institutional guidelines.

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

Event	**Action to Be Taken**
Grade 1 [a] *fever* [b] *with or without constitutional symptoms*	• Immediately interrupt the infusion • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate. • If symptoms recur, discontinue infusion of this dose • Administer symptomatic treatment, [c] including maintenance of IV fluids for hydration • In case of rapid decline or prolonged CRS (> 2 days) or in patients with significant symptoms and/or comorbidities, consider managing as per Grade 2. • For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS.
Grade 2 [a] *fever* [b] *with hypotension not requiring vasopressors and/or hypoxia requiring low-flow oxygen* [d] *by nasal cannula or blow-by*	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If symptoms recur, discontinue infusion of this dose • Administer symptomatic treatment [c] • For hypotension, administer IV fluid bolus as needed • Monitor cardiopulmonary and other organ function as clinically indicated and manage constitutional symptoms and organ toxicities as per institutional practice

	• Rule our 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 • Consider IV corticosteroids (e.g. methylprednisolone 2mg/kg/day or dexamethasone 10mg every 6 hours • Consider anti-cytokine therapy • Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manager as per Grade 3, that is, hospitalize patient (monitoring in the ICU recommended), permanently discontinue atezolizumab, and contact Medical Monitor • If symptoms resolve to Grade 1 or better for 3 consecutive days, 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 IRR and/or CRS • If symptoms do not resolve to Grade 1 or better for 3 consecutive days contact Medical Monitor
Grade 3 [a] *fever* [b] *with hypotension requiring a vasopressor (with or without vasopressin)* ***and/or*** *hypoxia requiring high-flow oxygen* [d] *by nasal cannula, face mask, non-rebreather mask, or venturi mask*	• Permanently discontinue atezolizumab. [e] • Administer symptomatic treatment. [c] • For hypotension, administer IV fluid bolus and vasopressor as needed. • Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. • Hospitalize patient until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for patients who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator and in consultation with the Medical Monitor.

Grade 4 [a] *fever* [b] *with hypotension requiring multiple vasopressors (excluding vasopressin)* ***and/or*** *hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)*	• Permanently discontinue atezolizumab. [e] • Administer symptomatic treatment. [c] • Admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. For patients who are refractory to anti-cytokine therapy, experimental treatments [f] may be considered at the discretion of the investigator and in consultation with the Medical Monitor. • Hospitalize patient until complete resolution of symptoms.

[a] Grading system for these management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE (version as specified in the protocol) should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.

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

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

[d] Low flow is defined as oxygen delivered at ≤ 6 L/min, and high flow is defined as oxygen delivered at > 6 L/min.

[e] 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.

[f] Refer to: Refer to Riegler et al. (2019).

Table 3. Management Guidelines for Gastrointestinal (GI) Toxicity

GI toxicity Immune-mediated colitis has been associated with the administration of atezolizumab. Management guidelines for diarrhea or colitis are provided below.

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

Event	Action to Be Taken
Diarrhea or colitis, Grade 1	• Continue atezolizumab. • Initiate symptomatic treatment. • Endoscopy is recommended if symptoms persist for > 7 days. • Monitor closely. • Hold abiraterone or enzalutamide
Diarrhea or colitis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset.[a] • Initiate symptomatic treatment. • Subject referral to GI specialist is recommended. • For recurrent events or events that persist > 5 days, consider treatment with 1-2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab.[b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c] • Hold abiraterone or enzalutamide
Diarrhea or colitis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset.[a] • Refer subject to GI specialist for evaluation and confirmatory biopsy if feasible. • Initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent • If event resolves to Grade 1 or better, resume atezolizumab.[b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab[c] • Hold abiraterone or enzalutamide. Treating investigator may resume abiraterone or enzalutamide if event resolves to Grade ≤ 1 **and/or** if event is deemed unrelated to abiraterone or enzalutamide after consultation with the Sponsor Principal Investigator.[d]
Diarrhea or colitis, Grade 4	• Hold abiraterone or enzalutamide. Treating investigator may resume abiraterone or enzalutamide if event resolves to Grade ≤ 1 **and/or** if event is deemed unrelated to abiraterone or enzalutamide after consultation with the Sponsor Principal Investigator.[d]

	• Permanently discontinue atezolizumab.[c] • Refer subject to gastrointestinal specialist for evaluation and confirmatory biopsy. • Initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

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

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re–challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate).

Table 4. Management Guidelines for Hepatic Events

Immune-mediated hepatitis has been associated with the administration of atezolizumab. Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in the table.

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

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

Event	Action to Be Taken
Hepatic event, Grade 1	• Continue atezolizumab and abiraterone or enzalutamide • Monitor Liver Function Tests (LFTs) weekly until values resolve to within normal limits.
Hepatic event, Grade 2	**All events:** • Hold atezolizumab and abiraterone or enzalutamide • Monitor LFTs more frequently until return to baseline values. **Events of > 5 days in duration:** • Withhold atezolizumab for up to 12 weeks after event onset.[a] • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b]

	• If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab.[c]
Hepatic event, Grade 3 or 4	• Permanently discontinue atezolizumab [c] • Hold abiraterone or enzalutamide. • Consider patient referral to GI specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Consider treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month

[a] Atezolizumab may be withheld for a longer periodof time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/dayoral prednisone. The acceptable length of the extendedperiodof time must be based on an assessment of benefit–risk by the investigator and in alignment with the protocolrequirements for the durationof treatment and documented by the investigator.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recoveredfrom the immune-mediated event. The decisionto re–challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documentedby the investigator (or an appropriate delegate).

Table 5. Management Guidelines for Pulmonary Events, Including Pneumonitis

Dyspnea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of atezolizumab. Patients will be assessed for pulmonary signs and symptoms throughout the study and will have computed tomography (CT) scans of the chest performed at every tumor assessment.

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. Management guidelines for pulmonary events are provided below.

Event	Action to Be Taken
Pulmonary event, Grade 1	• Continue atezolizumab and abiraterone or enzalutamide and monitor closely. • Re-evaluate on serial imaging. • Consider subject referral to pulmonary specialist. • For Grade 1 pneumonitis, consider withholding atezolizumab
Pulmonary event, Grade 2	• Continue abiraterone or enzalutamide • Withhold atezolizumab for up to 12 weeks after event onset.[a] • Refer subject to pulmonary and infectious disease specialists and consider bronchoscopy or BAL (bronchoalveolar lavage). • Initiate treatment with 1-2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab.[b]

	• If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Sponsor Principal Investigator.[c] • For recurrent events with no improvement after 48-72 hours of corticosteroids, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	• Permanently discontinue atezolizumab.[c] • Oral or IV broad-spectrum antibiotics should be administered in parallel to the immunosuppressive treatment. • Bronchoscopy or bronchoalveolar lavage is recommended. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

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

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re–challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or appropriate delegate).

Table 6. Management Guidelines for Immune-mediated Cardiac Events

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

All patients with possible myocarditis should be urgently evaluated by performing cardiac enzyme assessment, an ECG, a chest X-ray, an echocardiogram, and a cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. An endomyocardial biopsy may be considered to enable a definitive diagnosis and appropriate treatment, if clinically indicated.

Patients with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, should be treated according to the guidelines below.

IMMUNE-MEDIATED PERICARDIAL DISORDERS

Immune-mediated pericarditis should be suspected in any patient presenting with chest pain and may be associated with immune-mediated myocarditis (see section on myocarditis above).

Immune-mediated pericardial effusion and cardiac tamponade should be suspected in any patient presenting with chest pain associated with dyspnea or hemodynamic instability.

Patients should be evaluated for other causes of pericardial disorders such as infection (commonly viral), cancer related (metastatic disease or chest radiotherapy), cardiac injury related (post myocardial infarction or iatrogenic), and autoimmune disorders, and should be managed accordingly.

All patients with suspected pericardial disorders should be urgently evaluated by performing an ECG, chest X-ray, transthoracic echocardiogram, and cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. Pericardiocentesis should be considered for diagnostic or therapeutic purposes, if clinically indicated.

Patients with signs and symptoms of pericarditis, pericardial effusion, or cardiac tamponade, in the absence of an identified alternate etiology, should be treated according to the guidelines below. Withhold treatment with atezolizumab for Grade 1 pericarditis and conduct a detailed cardiac evaluation to determine the etiology and manage accordingly.

Event	Action to Be Taken

Immune-mediated myocarditis, Grades 2-4 Immune-mediated pericardial disorders, Grades 2–4	• Permanently discontinue atezolizumab. • Hold abiraterone or enzalutamide • Refer subject to cardiologist. • Initiate treatment per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, and VAD as appropriate. • Initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month and consider restarting abiraterone or enzalutamide at the same or modified dose based on recommendations from the consulting cardiologist and with permission from the Sponsor Principal Investigator.

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

Table 7. Management Guidelines for Endocrine Events

Endocrine events: Thyroid disorders, adrenal insufficiency, diabetes mellitus, and pituitary disorders have been associated with the administration of atezolizumab. Management guidelines for endocrine events are provided below.

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

Event	Action to Be Taken
Grade 1 hypothyroidism	• Continue atezolizumab • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely.

Grade 2 hypothyroidism	• Withhold atezolizumab and abiraterone or enzalutamide • Initiate treatment with thyroid-replacement hormone. • Monitor TSH closely. • Consider subject referral to endocrinologist. • Resume atezolizumab when symptoms are controlled, and thyroid function is improving. • Resume abiraterone or enzalutamide at the same or modified dose per investigator discretion when diagnosis of immune-related hypothyroidism is confirmed, and appropriate treatment is initiated or symptoms are controlled and thyroid function is improving.
Grade 3 and 4 hypothyroidism	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely. • Refer to an endocrinologist. • Admit patient to the hospital for developing myxedema (bradycardia, hypothermia, and altered mental status). • Resume atezolizumab when symptoms are controlled, and thyroid function is improving. • Permanently discontinue atezolizumab. [c]
Grade 1 hyperthyroidism	**TSH ≥ 0.1 mU/L and < 0.5 mU/L:** • Continue atezolizumab and abiraterone or enzalutamide • Monitor TSH every 4 weeks. • Consider patient referral to endocrinologist **TSH < 0.1 mU/L:** • Follow guidelines for Grade 2 symptomatic hyperthyroidism. • Consider patient referral to endocrinologist
Grade 2 hyperthyroidism	• Withhold atezolizumab and abiraterone or enzalutamide • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Consider subject referral to endocrinologist. • Resume atezolizumab when symptoms are controlled, and thyroid function is improving. • Permanently discontinue atezolizumab and contact Sponsor Principal Investigator for life-threatening immune-related hyperthyroidism. [c] • Resume abiraterone or enzalutamide at the same or modified dose per investigator discretion when diagnosis of immune-related hypothyroidism is confirmed, and appropriate treatment is initiated or symptoms are controlled and thyroid function is improving.

Grade 3 and 4 hyperthyroidism	• Withhold atezolizumab. • Initiate treatment with anti-thyroid drugs such as methimazole or carbimazole as needed. • Refer to an endocrinologist. • Resume atezolizumab when symptoms are controlled, and thyroid function is improving. • Permanently discontinue atezolizumab. [c]
Symptomatic adrenal insufficiency, Grades 2-4	• Withhold atezolizumab for up to 12 weeks after event onset.[a] • Refer subject to endocrinologist. • Perform appropriate imaging. • Initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better and subject is stable on replacement therapy, resume atezolizumab.[b] • If event does not resolve to Grade 1 or better or subject is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab and contact Sponsor Principal investigator.[c] • Hold abiraterone or enzalutamide and refer to endocrinologist as per above. Abiraterone or Enzalutamide may be resumed at the same or modified dose at the discretion of the investigator if appropriate treatment is initiated and symptoms are controlled with resolution to Grade 1 or better.
Hyperglycemia, Grade 1 or 2	• Continue atezolizumab. • Investigate for diabetes. If patient has Type 1 diabetes, treat as a Grade 3 event. If patient does not have Type 1 diabetes, treat as per institutional guidelines. • Monitor for glucose control. • Continue abiraterone or enzalutamide.
Hyperglycemia, Grade 3 or 4	• Withhold atezolizumab and abiraterone or enzalutamide. • Initiate treatment with insulin. • Evaluate for diabetic ketoacidosis and manager as per institutional guidelines • Monitor for glucose control. • Resume atezolizumab and abiraterone or enzalutamide when symptoms resolve, and glucose levels are stable after consultation with the endocrinologist and Sponsor Principal Investigator.
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset.[a] • Refer subject to endocrinologist. • Perform brain MRI. • Initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement.

	• Initiate hormone replacement if clinically needed. • If event resolves to Grade 1 or better, resume atezolizumab.[b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Sponsor Principal Investigator.[c] • For recurrent hypophysitis, treat as a Grade 4 event. • Continue abiraterone or enzalutamide.
Hypophysitis. Grade 4 (pan-hypopituitarism), Grade 4	• Permanently discontinue atezolizumab and contact Sponsor Principal Investigator.[c] • Refer subject to endocrinologist. • Perform brain MRI. • Initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement as clinically needed. • Hold abiraterone or enzalutamide and resume • If event resolves to Grade ≤ 2 and/or if event is deemed unrelated to abiraterone or enzalutamide. In case of uncertain relationship and/or recurrent Grade 4 hypophysitis, rechallenge with abiraterone or enzalutamide at the same or modified dose might be considered after consultation with the Sponsor Principal Investigator.[d]

MRI=magnetic resonance imaging; TSH=thyroid-stimulating hormone.

[a] Atezolizumab may be withheld for a longer periodof time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/dayoral prednisone. The acceptable length of the extendedperiodof time must be based on an assessment of benefit–risk by the investigator and in alignment with the protocolrequirements for the durationof treatment and documented by the investigator.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re–challenge patients with atezolizumab shouldbe based on investigator's assessment of benefit–risk and documentedby the investigator (or an appropriate delegate).

Table 8. Management Guidelines for Dermatologic Events

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

Event	Action to Be Taken
Dermatologic event, Grade 1	• Continue atezolizumab and abiraterone or enzalutamide • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).

Dermatologic event Grade 2	• Continue atezolizumab and abiraterone or enzalutamide • Consider subject referral to dermatologist. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve. • If unresponsive to topical corticosteroids, consider oral prednisone 0.5 mg/kg/day
Dermatologic event, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset.[a] • Refer subject to dermatologist. • 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. • If event resolves to Grade 1 or better, resume atezolizumab.[b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Sponsor Principal Investigator.[c] • Consider withholding abiraterone or enzalutamide per investigator discretion • Resume abiraterone or enzalutamide if event resolves to Grade ≤ 2 and/or if event is deemed unrelated to abiraterone or enzalutamide. In case of uncertain relationship and/or recurrent Grade 3 dermatologic event, rechallenge with abiraterone or enzalutamide might be considered after consultation with the Sponsor Principal Investigator.[d]
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and contact Sponsor Principal Investigator.[c] • Consider withholding abiraterone or enzalutamide. • Resume abiraterone or enzalutamide if event resolves to Grade ≤ 2 and/or if event is deemed unrelated to abiraterone or enzalutamide. In case of uncertain relationship and/or recurrent Grade 4 dermatologic event, rechallenge with abiraterone or enzalutamide might be considered after consultation with the Sponsor Principal Investigator.[d]
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	**Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis:** • Withhold atezolizumab for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis. • Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist, or urologist as relevant) for evaluation and, if indicated, biopsy. • Follow the applicable treatment and management guidelines above. • If Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed, permanently discontinue atezolizumab.

[a] Atezolizumab may be withheld for a longer periodof time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/dayoral prednisone. The acceptable length of the extendedperiodof time must be based on an assessment of benefit–risk by the investigator and in alignment with the protocolrequirements for the durationof treatment and documented by the investigator.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re–challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate).

Table 9. Management Guidelines for Neurologic Disorders

Neurologic disorders: Myasthenia gravis and Guillain-Barré syndrome have been observed with single-agent atezolizumab. Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic workup is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided below, with specific guidelines for myelisitis provided.

Event	Action to Be Taken
Immune-mediated neuropathy, Grade 1	• Continue atezolizumab and abiraterone or enzalutamide • Investigate etiology. • Any cranial nerve disorder (including facial paresis) should be managed as per Grade 2 management guidelines below.
Immune-mediated neuropathy, including facial paresis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset.[a] • Investigate etiology and subject to neurologist. • Initiate treatment as per institutional guidelines. • For general immune-mediated neuropathy: – If event resolves to Grade 1 or better, resume atezolizumab. [b] – If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c] • For facial paresis: – If event resolves fully, resume atezolizumab [b] ○ If event does not resolve fully while withholding atezolizumab, permanently discontinue atezolizumab. [c] • Continue abiraterone or enzalutamide.
Immune-mediated neuropathy, including facial paresis, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Sponsor Principal Investigator.[c] • Refer patient to neurologist • Initiate treatment as per institutional guidelines. • Consider withholding abiraterone or enzalutamide. • Resume abiraterone or enzalutamide if event resolves to Grade ≤ 2 and/or if event is deemed unrelated to abiraterone or enzalutamide. In case of uncertain relationship and/or recurrent Grade 3 or 4 neuropathy, rechallenge with abiraterone or enzalutamide might be considered after consultation with the Sponsor Principal Investigator.[d]

Myasthenia gravis and Guillian-Barre syndrome (any grade)	• Permanently discontinue atezolizumab and contact Medical Monitor.[c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of corticosteroids equivalent to 1−2 mg/kg/day oral or IV prednisone.

[a] Atezolizumab may be withheld for a longer periodof time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/dayoral prednisone. The acceptable length of the extendedperiodof time must be based on an assessment of benefit−risk by the investigator and in alignment with the protocolrequirements for the durationof treatment and documented by the investigator.

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

a. [c]Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re−challenge patients with atezolizumab should be based on investigator's assessment of benefit−risk and documented by the investigator (or an appropriate delegate). Approval by the Sponsor Principal Investigator must be documented.

Table 10 Management Guidelines for Immune-Mediated Myelitis

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

Table 1. Management Guidelines for Ocular Events

Ocular Event: An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). Management guidelines for ocular events are provided below.	
Event	**Action to Be Taken**
Ocular event, Grade 1	• Continue atezolizumab. • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If symptoms persist, treat as a Grade 2 event.
Ocular event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c]
Ocular event, Grade 3 or 4	• Permanently discontinue atezolizumab. [c] • Refer patient to ophthalmologist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

Table 2. Management Guidelines for Pancreatic Events

Pancreatic Events: Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate workup should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided below.

Event	Action to Be Taken
Amylase and/or lipase elevation, Grade 2	**Amylase and/or lipase > 1.5–2.0 × ULN:** • Continue atezolizumab. • Monitor amylase and lipase weekly. • For prolonged elevation (e.g., > 3 weeks), consider treatment with corticosteroids equivalent to 10 mg/day oral prednisone. **Asymptomatic with amylase and/or lipase > 2.0–5.0 × ULN:** • Treat as a grade 3
Amylase and/or lipase elevation, Grade 3 or 4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Monitor amylase and lipase every other day. • If no improvement, consider treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Immune-mediated pancreatitis, Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Immune-mediated pancreatitis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to GI specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

GI= gastrointestinal.

[a] Atezolizumab may be withheld for a longer periodof time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/dayoral prednisone. The acceptable lengthof the extendedperiodof time must be based on an assessment of benefit–risk by the investigator and in alignment with the protocolrequirements for the durationof treatment and documented by the investigator.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recoveredfrom the immune-mediated event. The decisionto re–challenge patients with atezolizumab should be based on investigator'sassessment of benefit–risk and documented by the investigator (or an appropriate delegate).

Table 3. Management Guidelines for Immune-mediated Meningoencephalitis

Immune-mediated meningoencephalitis is an identified risk associated with the administration of atezolizumab. Immune-mediated meningoencephalitis should be suspected in any patient presenting with signs or symptoms suggestive of meningitis or encephalitis, including, but not limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction, and altered or depressed level of consciousness. Encephalopathy from metabolic or electrolyte imbalances needs to be distinguished from potential meningoencephalitis resulting from infection (bacterial, viral, or fungal) or progression of malignancy, or secondary to a paraneoplastic process.

All patients being considered for meningoencephalitis should be urgently evaluated with a CT scan and/or MRI scan of the brain to evaluate for metastasis, inflammation, or edema. If deemed safe by the treating physician, a lumbar puncture should be performed, and a neurologist should be consulted.

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines below

Event	Action to Be Taken
Immune-mediated meningoencephalitis, all grades	• Permanently discontinue atezolizumab. [a] • Refer patient to neurologist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate).

Table 4. Management Guidelines for Renal Events

Renal Events: Immune-mediated nephritis has been associated with the administration of atezolizumab. Eligible patients must have adequate renal function. Renal function, including serum creatinine, should be monitored throughout study treatment. Patients with abnormal renal function should be evaluated and treated for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as non-steroidal anti-inflammatory drugs). Refer the patient to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

Patients with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines.

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

[a] Atezolizumab may be withheld for a longer periodof time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/dayoral prednisone. The acceptable length of the extendedperiodof time must be based on an assessment of benefit–risk by the investigator and in alignment with the protocolrequirements for the durationof treatment and documented by the investigator.

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

[c] Resumption of atezolizumabmay be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re–challenge patients with atezolizumab shouldbe based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate).

Table 5. Management Guidelines for Immune-mediated Myositis

Immune-mediated myositis has been associated with the administration of atezolizumab. Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are among the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatine kinase increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle biopsy. Patients with possible myositis should be referred to a rheumatologist or neurologist. Patients with possible myositis should be monitored for signs of myocarditis.

Patients with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines.

Event	Action to Be Taken
Immune-mediated myositis, Grade 1	• Continue atezolizumab. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines.
Immune-mediated myositis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a]. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Consider treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact sponsor principal investigator. [c]

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

[a] Atezolizumab may be withheld for a longer periodof time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/dayoral prednisone. The acceptable length of the extendedperiodof time must be based on an assessment of benefit–risk by the investigator and in alignment with the protocolrequirements for the durationof treatment and documented by the investigator.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re–challenge patients with atezolizumab should be based on investigator's assessment of benefit–riskand documentedby the investigator (or an appropriate delegate).

Table 6. Management Guidelines for Hemophagocytic Lymphohistiocytosis (HLH) or Macrophase Activation Syndrome (MAS)

Hemophagocytic lymphohistiocytosis (HLH) or macrophase activation syndrome (MAS): 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

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

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

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

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

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

Patients with suspected HLH or MAS should be treated according to the guidelines below.

Event	Action to Be Taken
Suspected HLH or MAS	• Permanently discontinue atezolizumab. • Consider patient referral to hematologist. • Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines.

	• Consider initiation of IV corticosteroids, an immunosuppressive agent, and/or anti-cytokine therapy. • If event does not respond to treatment within 24 hours, initiate treatment as appropriate accordingto published guidelines (La Rosée 2015; Schram and Berliner 2015; La Rosée et al. 2019). • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

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7. SAFETY EVALUATION

7.1 Definitions

7.1.1 Adverse Events

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution.
This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with mHSPC that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations).
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

7.1.2 Serious Adverse Events

An AE should be classified as an SAE if the following criteria are met:

- It results in death (i.e., the AE causes or leads to death).
- It is life threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
- It requires or prolongs inpatient hospitalization [note, a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event) or admission for an elective surgery, planned prior to signing consent are not considered SAEs].
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

7.1.3 Adverse Events of Special Interest

AESIs are a subset of Events to Monitor (EtMs) of scientific and medical concern specific to the product, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is required. Such an event might require further investigation

in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial Sponsor to other parties (e.g., Regulatory Authorities) may also be warranted.

The atezolizumab Events of Special Interest Are:

The following AEs are considered of special interest and must be reported to the PCCTC expeditiously, irrespective of regulatory seriousness criteria:

- 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 and based on the following observations:

  Treatment-emergent ALT or AST $> 3 \times$ ULN (or $> 3\times$ baseline value in disease states where LFTs may be elevated at baseline) in combination with total bilirubin $> 2\times$ ULN (of which $\geq 35\%$ is direct bilirubin).

  Treatment-emergent ALT or AST $> 3 \times$ ULN (or $> 3\times$ baseline value in disease states where LFTs may be elevated at baseline) in combination with clinical jaundice.

- Suspected transmission of an infectious agent by the study treatment, defined as:

  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 subject exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.

- Systemic lupus erythematosus
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine release syndrome, macrophage activating syndrome and hemophagocytic lymphohistiocytosis
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)
  - Myelitis
  - Facial paresis

7.2 Risks Associated with atezolizumab

For additional information, please refer to the current version of the atezolizumab Investigator's Brochure (IB).

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

7.3 Methods and Timing for Assessing and Recording Safety Variables

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, are collected and reported to appropriate IRB(s) and the PCCTC. The PCCTC will report SAEs to the sponsor and Genentech within one business day of receipt.

7.3.1 Adverse event reporting period

The study period during which AEs, AESIs, and special situations must be reported begins after informed consent is obtained and ends 90 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier.

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

7.3.2 Assessment of adverse events

All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to study treatments (see following guidance), and actions taken.
To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

Yes (possible/probable/definite/unlikely)
There is a plausible temporal relationship between the onset of the AE and administration of the atezolizumab, and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the atezolizumab or with similar treatments; and/or the AE abates or resolves upon discontinuation of the [study drug] or dose reduction and, if applicable, reappears upon re- challenge.

No (unrelated)
Evidence exists that the AE has an etiology other than the {study drug} (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to {study drug} administration (e.g., cancer diagnosed 2 days after first dose of study drug).
Expected adverse events are those adverse events that are listed or characterized in the Package Insert (P.I.) or current IB for the study treatments.

Unexpected adverse events are those not listed in the P.I. or current IB. or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or IB. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or IB. only referred to elevated hepatic enzymes or hepatitis.
For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

7.4 Procedures for Eliciting, Recording, and Reporting Adverse Events

7.4.1 Eliciting adverse event information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all subject 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?"

7.4.2 Specific Instructions for recording adverse events

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

7.4.2.1 *Diagnosis versus signs and symptoms*

If known at the time of reporting, a diagnosis should be reported 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, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

7.4.2.2 *Deaths*

All deaths that occur during the protocol-specified AE reporting period (see Section 7.3.1), regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report “Unexplained Death”.

7.4.2.3 *Preexisting medical conditions*

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

7.4.2.4 *Hospitalizations for medical or surgical procedures*

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure because of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For

example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE. Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study

7.4.2.5 *Assessment of severity of adverse events*

The adverse event severity grading scale for the NCI CTCAE 5.0 will be used for assessing adverse event severity. Table 16 should be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

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

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

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

Note: Based on the most recent version of NCI CTCAE 5.0, which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

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

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

[c] If an event is assessed as a "significant medical event," it must be reportedas a serious adverse event

[d] Grade 4 and 5 events must be reported as serious adverse events

7.4.2.6 *Post-study adverse events*

The investigator should expeditiously report any SAE occurring after a subject has completed or discontinued study participation if attributed to prior atezolizumab exposure.

7.5 Adverse Event Reporting

All AEs must be reported in routine study data submissions on the toxicity case report forms. AEs reported through expedited processes (e.g., via SAE Form, etc.) must also be reported in routine

study data submissions. Investigators and study teams must report all SAEs to the PCCTC within the timelines described below.
The PCCTC will report all SAEs received from Investigators and study teams to Genentech within one business day upon receipt.

Serious adverse events (SAEs) and AEs of special interest (AESIs), and special situation reports where the subject has been exposed to the study treatment will be sent on an SAE form. Transmission of these reports (initial and follow-up) will be sent within the timelines specified below:

- AESIs: AESIs shall be forwarded to the PCCTC within fifteen (15) calendar days of the awareness date.

  Relevant follow-up information should be submitted to the PCCTC as soon as it becomes available.

- Special Situation Reports: In addition to all AEs and AESIs, the following Special Situations Reports should be collected and transmitted to the PCCTC even in the absence of an Adverse Event within thirty (30) calendar days:

  - Data related to overdose, abuse, off-label use, misuse, inadvertent/erroneous administration, medication error (including potentially exposed in case of medication errors or intercepted medication errors)
  - Drug interaction
  - In addition, reasonable attempts should be made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population

Product Complaints

- All Product Complaints (with or without an AE) shall be forwarded to the PCCTC within thirty (30) calendar days of the awareness date.

- A Product Complaint is defined as any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial.

7.5.1 SAE Form reporting guidelines

The following information should be included on the SAE form:

- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

7.5.1.1 *Follow-up information*

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original SAE Form report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original SAE form

7.5.2 Reporting to regulatory authorities, ethic committees and investigators

7.5.2.1 *Site Responsibilities*

Participating sites are responsible for reporting SAEs to the PCCTC within 24 hours or 1 business day. All SAEs must be reported to the site's IRB per current institutional standards.

PCCTC Contact Information:
Prostate Cancer Clinical Trials Consortium
Email: pcctc@mskcc.org

7.5.2.2 *Sponsor Responsibilities*

Genentech as the Marketing Authorization Holder will be responsible for the reporting of individual case safety reports from the study to the regulatory authority in compliance with applicable regulations.

The PCCTC on behalf of the Sponsor will report SAEs to Genentech. SAEs, whether related or not related to study drug will be reported to Genentech within 24 hours or one business day of becoming aware of the event. SAEs must be recorded on the SAE form.

The PCCTC will be responsible for the distribution of safety information to sites for distribution to local IRBs.

For questions related to safety reporting, please contact Genentech Drug Safety:

Tel: (888) 835-2555
Fax: (650) 225-4682 or (650) 225-4630

7.5.3 Reporting to Genentech:

7.5.3.1 *Case Transmission Verification of Single Case Reports*

The Investigator agrees to conduct the Case Transmission verification to ensure that all single case reports have been adequately received by Genentech via the PCCTC emailing Genentech a Quarterly line-listing documenting single case reports sent by the PCCTC to Genentech in the preceding time period. The periodic line-listing will be exchanged within seven (7) calendar days of the end of the agreed time period. Confirmation of receipt should be received within the time period mutually agreed upon.

If discrepancies are identified, the Sponsor and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution. The sponsor shall receive reconciliation guidance documents within the 'Activation Package'.
Following Case Transmission Verification, single case reports which have not been received by Genentech shall be forwarded by the PCCTC to Genentech within five (5) calendar days from request by Genentech.
At the end of the study, a final cumulative Case Transmission Verification report will be sent to Genentech.
Monthly or quarterly line-listings, Non-serious line listings and cumulative/final CTV should be sent to ctvistsa@gene.com

7.5.3.2 *Exchange of Single Case Reports*

The PCCTC will be responsible for collecting all protocol-defined Adverse Events (AEs)/Serious Adverse Events (SAEs), AEs of Special Interest (AESIs), Special Situation Reports (including pregnancy reports) and Product Complaints (with or without an AE) originating from the Study for the Product.

The PCCTC must report all the above-mentioned single case reports adequately to Genentech within the timelines described below. The completed Genentech approved reporting forms should be faxed/emailed immediately upon completion to Genentech at the following contacts:
All protocol-defined AEs, SAEs, AESIs, Special Situation Reports (including pregnancy reports) and Product Complaints with an AE should be sent to:

Fax: 650-238-6067
Email: usds_aereporting-d@gene.com

All Product Complaints without an AE should be reported to:

PC Hotline Number: (800) 334-0290 (M-F: 5 am to 5 pm PST)
It is understood and agreed that the Sponsor will be responsible for the evaluation of AEs/SAEs, AESIs, Special Situation Reports (including pregnancy reports) and Product Complaints (with or without an AE) originating from the study.

These single case reports will be exchanged between the parties as outlined below so that regulatory obligations are met.

Serious adverse events (SAEs), AEs of Special Interest (AESIs), pregnancy reports (i.e., pregnancy occurring in the partner of a male study subject), other Special Situation Reports and Product Complaints (with or without an AE), where the patient has been exposed to the Genentech Product, will be sent on a on Genentech approved reporting forms to Genentech Drug Safety.

Transmission of these reports (initial and follow-up) will be either electronically or by fax and within the timelines specified below:

Serious Adverse Drug Reactions (SADRs)	*1 business day of the awareness date*
Other SAEs	*1 business day* of the awareness date
Special Situation Reports (With or without AE)	30 calendar days of the awareness date.
Product Complaints (With or without AE)	30 calendar days of the awareness date.
AESIs	30 calendar days of the awareness date.

- **SADRs**
  Serious AE reports that are related to the Product shall be transmitted to Genentech within 1 business day of the awareness date.

- **Other SAEs**
  Serious AE reports that are unrelated to the Product shall be transmitted to Genentech within 1 business day of the awareness date.

- **AESIs**
  AESIs shall be forwarded to Genentech within thirty (30) calendar days of the awareness date.

- **Other Special Situation Reports**
  The following other Special Situations Reports should be collected even in the absence of an Adverse Event and transmitted to Genentech within thirty (30) calendar days:
  - Data related to overdose, abuse, misuse or medication error (including potentially exposed or intercepted medication errors)
  - In addition, reasonable attempts should be made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population

- **Product Complaints**
  All Product Complaints (with or without an AE) shall be forwarded to Genentech within thirty (30) calendar days of the awareness date.

  A Product Complaint is defined as any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial.

- **Reporting to Regulatory Authorities, Ethics Committees and Investigators**

The sponsor will be responsible for the expedited reporting of safety reports originating from the Study to the Institutional Review Boards (IRB), where applicable (see section 12.3).

The sponsor will be responsible for the distribution of safety information to its own investigators, where relevant, in accordance with local regulations.

7.5.3.3 Aggregate Reports: Data and Safety Monitoring

The Data and Safety Monitoring Plans (DSMP) at MSKCC were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials. The DSMPs at MSKCC were established and are monitored by the Office of Clinical Research.

There are several different mechanisms by which clinical trials are monitored for data, safety, and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research quality assurance) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. There are several committees: Data and Safety Monitoring Committee (DSMC) for Phase I and II clinical trials, and the Data and Safety Monitoring Board (DSMB) for Phase III clinical trials, report tothe MSKCC Research Council and Institutional Review Board. As a moderate risk trial, this study will be monitored by DSMC twice per year.

MSKCC, as the Sponsor of the Study, will be responsible for the preparation of their own Data Safety Monitoring Committee Report for the study and for the submission of the report to the local IRB. The sponsor will share a copy of their own DSMC report with Genentech as soon as reasonably possible after completion.

Final Study Report:
The PCCTC will forward a copy of the Final Study Report to Genentech upon completion of the Study and forward a copy of the Publication to Genentech upon completion of the Study.

Study Close Out:
Any literature articles that are a result of the study should be sent to Genentech. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study: anti-pdl-1-mpd3280a-gsur@gene.com
And to Genentech Drug Safety CTV oversight mailbox at: ctvistsa @gene.com

Queries:
Queries related to the Study will be answered by Sponsor (MSK). However, responses to all safety queries from regulatory authorities, Ethics Committees and Institutional Review Board or for publications will be discussed and coordinated between the Parties. The Parties agree that Genentech shall have the final say and control over safety queries relating to the Product. Sponsor (MSK) agrees that it shall not answer such queries from regulatory authorities and other sources relating to the Product independently but shall redirect such queries to Genentech.

The Sponsor and Genentech will use all reasonable effort to ensure that deadlines for responses to urgent requests from Regulatory Authorities and/or IRB/IEC for information or review of data are met. The Sponsor and Genentech will clearly indicate on the request the reason for urgency and the date by which a response is required.

Signal Management and Risk Management
Genentech is responsible for safety signal management (signal detection and/or evaluation) for their own Product. However, it is agreed that MSK, as a Sponsor will be primarily responsible for assessment of the benefit-risk balance of the Study.

If Sponsor (MSK) issues a safety communication relevant for Genentech (i.e., a safety issue that notably impacts the benefit-risk balance of the Study and / or triggers any changes to the Study) this will be sent to Roche within five (5) business days of its internal approval.

As needed, Genentech will reasonably assist Sponsor (MSK) with signal and risk management activities related to the Product within the Study.

COMPLIANCE WITH PHARMACOVIGILANCE AGREEMENT / AUDIT

Genentech and the participating sites shall follow their own procedures for adherence to AE reporting timelines.

The Parties (Genentech and MSKCC) shall monitor and, as applicable, request feedback from the other Party regarding AE report timeliness in accordance with its own procedures. The Parties agree to provide written responses in a timely manner to inquiries from the other Party regarding AE reports received outside the agreed upon protocol timelines. If there is any detection of trends of increasing or persistent non-compliance to transmission timelines stipulated in this protocol, both Parties agree to conduct ad hoc or institute a regular joint meeting to address the issue.

In case of concerns related to non-compliance of processes, other than exchange timelines, with this Protocol, the Parties will jointly discuss and collaborate on clarifying and resolving the issues causing non-compliance. Every effort will be made by the non-compliant Party to solve the non-compliance issues and inform the other Party of the corrective and preventative actions taken.

Upon justified request, given sufficient notice of no less than sixty (60) calendar days, an audit under the provisions of this protocol can be requested by either Party. The Parties will then discuss and agree in good faith upon the audit scope, agenda and execution of the audit. The requesting Party will bear the cost of the audit.

8. CRITERIA FOR OUTCOME ASSESSMENT

8.1 Outcome Assessment

All baseline evaluations will be performed as closely as possible to the beginning of treatment (within 28 days of treatment start for CT Chest/Abdomen Pelvis, Bone Scan). For subsequent evaluations, the method of assessment and techniques will be the same as those used at baseline.

8.2 Assessment of Treatment Failure (Definition of Progression)

Treatment failure is defined as one of the following:

1) Biochemical failure as defined by STAMPEDE

A unique threshold PSA value for biochemical failure is calculated, referred to as the **PSA progression value,** based on the STAMPEDE trial.[7]

This value is derived for each subject based on their PSA nadir, defined as the lowest PSA value reported between treatment start and the first 24 weeks on trial. Please refer to the PSA progression value calculator on the STAMPEDE website.

The exact method for deriving the progression value for a subject depends on the value of their PSA nadir, and how this compares to their pre-treatment PSA value (i.e., the extent of the fall in PSA from the starting point).

The PSA progression value is calculated in one of three ways:

A. If the lowest recorded PSA value in the first 24 weeks following treatment start is more than 4ng/ml and more than 50% of the pre-treatment PSA level, then the subject fulfils the criteria for immediate treatment failure.

B. For subjects whose PSA nadir in the first 24 weeks following treatment start is less than or equal to 50% of the pre-treatment PSA level but remains above 4ng/ml, biochemical failure will be defined as a rise of 50% above the nadir level.
C. For subject whose PSA nadir is less than or equal to 4ng/ml, biochemical failure is defined as at least a 50% rise above the nadir value that is also above 4ng/ml.

Confirming biochemical failure: the timing of assessments needs to be considered because spurious rises in PSA can occur e.g., following procedures involving the urinary tract. For this reason, any isolated rise in PSA should be confirmed before reporting biochemical failure.

In the case that the raised PSA value reaches the progression value, a confirmatory PSA test should be performed between one week and 3 months later. Biochemical failure is confirmed if the second value is around the same level or higher i.e. the trend is confirmed. The date of PSA progression should be provided as the date of the first raised PSA that fulfilled the trial definition of progression. Only the first instance of biochemical failure needs to be reported. A confirmatory PSA is not required if there are other signs of progression e.g., progression of cancer related symptoms (clinical progression) or new radiological progression. Study treatment should continue during confirmation of progression.

Second line treatment commenced specifically for biochemical failure should not start until the trial definition for biochemical failure has been met. However, if second line treatment does start before the trial definition is met then report the closest PSA value prior to the treatment start date as the progression value. This is not required if second line treatment is being started for other signs of progression e.g. clinical or radiological.

2) Radiographic progression as defined by Prostate Cancer Working Group 3. (PCWG3)[38] Please reference PCWG3 for definitions.[38] **Testosterone levels:** are only required when reporting biochemical progression whilst receiving hormone treatment to confirm the diagnosis of castrate resistant prostate cancer. Testosterone levels are not required when reporting biochemical progression in subjects not receiving hormone therapy e.g., subjects who presented with non-metastatic disease have relapsed following completion of treatment.
3) Death from any cause: death from other causes is considered a competing event

See Appendix F for further details on the trial definition of biochemical failure.

9. DATA REPORTING AND REGULATORY REQUIREMENTS

9.1 Data Collection and Management

Data collected during this study will be entered into a secure database.

9.1.1 Electronic Case Report Forms (eCRFs)

Standardized eCRFs and CRF Completion Guidelines will be created by the PCCTC for the collection of study data. Access and training for PCCTC Medidata Rave EDC will be made available to participating sites upon local regulatory approval. The participating site investigator is responsible for ensuring eCRFs are completed accurately and in a timely manner.

9.1.2 Source documents

Source documentation refers to original records of observations, clinical findings and evaluations that are subsequently recorded as data. Source documentation will be made available to support the subject's research record.

9.1.3 Record retention

The investigator will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. After study closure, the investigator will maintain all source documents and study-related documents. Records are to be retained and securely stored until the later of: (a) two (2) years following the date a New Drug Application is approved for the Study Drug that is the subject of the Clinical Trial; or (b) two (2) years after the Investigational New Drug Application for such Study Drug is terminated or withdrawn, or such longer period of time as may be required by Participant policies, applicable laws, rules or regulations.

9.2 Study Monitoring and Quality Assurance

9.2.1 Data and Safety Monitoring

The Data and Safety Monitoring Plans (DSMP) at Memorial Sloan Kettering Cancer Center (Sponsor) were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials. The DSMPs at MSK were established and are monitored by the Office of Clinical Research.

There are several different mechanisms by which clinical trials are monitored for data, safety, and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research quality assurance) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. There are several committees: Data and Safety Monitoring Committee (DSMC) for phase I and phase II clinical trials, and the Data and Safety Monitoring Board (DSMB) for phase III clinical trials, report to the MSK Research Council and Institutional Review Board. As a moderate risk trial, this study will be monitored by DSMC twice per year.

9.2.2 Data Monitoring, Auditing, and Quality Assurance

In addition to review by DSMC PCCTC will conduct regularly scheduled monitoring visits. Reports will be generated by the PCCTC to monitor subject accruals and the completeness of data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and the extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period, and potential problems will be brought to the attention of the Sponsor Principal Investigator for discussion and action.

The monitoring visit will include a review of source documentation to evaluate:

- Regulatory/IRB compliance (review of current protocol and amendments, Informed consent documents and procedures, annual continuing review reports, AEs/SAEs)
- Protocol defined treatment compliance

- Subject records
  - A signed and dated informed consent form for each subject
  - Adherence to eligibility criteria
  - Source Data Verification for identified subjects

Monitoring findings will be reviewed and disseminated to the site investigators and staff.

The PCCTC may also perform site audits. If a site is notified of an external audit relating to this study, the site should notify the PCCTC immediately. The PCCTC and/or Monitors assigned to this study will provide site support during audits (quality control and/or regulatory agency) including review and assisting sites with responses to audit findings.

9.2.3 Data Review and Queries

The PCCTC will review data and source documentation. Data will be monitored, and source data verified as defined in the Monitoring and/or Data Management plans and discrepancies will be issued as queries in the EDC. In addition, the PCCTC will review data for logic, consistency, and obvious anomalies.

10. STATISTICAL CONSIDERATIONS

The primary objective is to evaluate the failure-free rate at 2 years (binary endpoint). Failure is defined as: biochemical failure (see Appendix F and Section 8); radiographic progression defined by PCWG3; or death from any cause. Subjects who are lost to follow-up or withdraw will be considered to have had biochemical failure. Subjects who stop treatment due to toxicity will not be considered failures and will be followed for the primary endpoint. We anticipate very few subjects will be lost to follow-up. The evaluable subjects are those who received at least 1 dose of atezolizumab. Subjects who do not receive at least one dose of atezolizumab will be replaced. To this end we will use a single-stage design. Accrual will continue until there are 42 evaluable subjects who have taken at least one dose of atezolizumab. We estimate to accrue a total of 44 subject in order to reach the goal of 42 evaluable subjects. If there are more than 42 evaluable subjects, then we will only count the first 42 towards primary analysis. We will declare the treatment regimen worthy of further investigation if at least 34 among the 42 subjects remain failure free at 2 years. If, at any time during the protocol, the 9th failure occurs then the trial will be stopped early for futility. Although we have altered the treatment regimen, data for patients with castrate-sensitive prostate cancer do not show any efficacy difference between Abiraterone and Enzalutamide. Thus, we do not believe the original effect size presumptions and stopping rules need modification. This decision rule has a type 1 error rate of 0.08 when the true 2-year failure-free rate is at most 70%, and a type 2 error rate of 0.06 when the true 2-year failure-free rate is at least 88%. The 2 year FFS in STAMPEDE was 70% for the metastatic cohort and the 2 year rPFS and OS in LATITUDE was 65% and 80% respectively. [6-7]

To ensure subject safety, we will continuously monitor toxicity profiles and implement a sequential stopping rule as follows. If ≥ 9 out of the first 10, or ≥ 16 out of the first 20, or ≥ 22 out of the first 30, or ≥ 31 out of the total 42 subjects have any acute grade ≥ 3 treatment-related toxicities (including both hematologic and non-hematologic toxicity), then the trial will be stopped, and all adverse events will be thoroughly examined by the investigators. This sequential stopping rule is based on the STAMPEDE and LATITUDE trials of abiraterone and ADT, and we would view an acceptable rate of acute grade ≥ 3 treatment-related toxicity evaluated at C8D1 as

0.55. The probability table below shows the likelihood of stopping the trial at various true rates of acute grade ≥ 3 treatment-related toxicity.

True acute grade 3-5 toxicity rate	0.50	0.55	0.60	0.65	0.70	0.75	0.80
Probability of early stopping	2.0%	5.5%	13.8%	29.4%	52.2%	76.2%	92.9%

For OS analysis, all subjects receiving at least 1 dose of atezolizumab will be analyzed by the Kaplan-Meier method. Prostate cancer-specific mortality will be evaluated using the cumulative incidence function estimates (death from other causes is considered as a competing event). Adverse events will be collected for the entire time the subject is on protocol mandated therapy using CTCAE v 5.0 and will be tabulated and summarized by type and grade. All subjects will be counted towards this objective. The symptomatic skeletal events (SSEs) include pathological fracture, spinal cord compression, requirement for RT to bone (e.g. for pain or impending fracture) and requirement for surgery (e.g. for prevention or management of fracture). Such SSEs will also be tabulated and summarized descriptively, and all subjects will be analyzed.

For exploratory objectives, several tissue and blood-based measures will be correlated with response of treatment. Response will be defined as a binary endpoint; in which a subject is free from failure at 2 years. Measures to be correlated include biopsy specimens such as diagnostic baseline prostate biopsy and prostate biopsy at time of fiducial placement as well as optional biopsies of metastatic sites. Fisher tests will be used. Tumor mutation burden (TMB) using institutional gene profiling assays, gene expression profiles of tumor microenvironment using RNA Sequencing (RNAseq), immunohistochemistry (IHC) analysis of tumor infiltrating lymphocytes and PDL1 expression will also be correlated with response using Fisher tests. Peripheral blood specimens (at C1D1, C2D1, C4D1, C6D1, and POD) will be assessed and changes in T cell phenotype and MDSC populations, TCR richness and diversity, immunophenotypic changes via CyTOF will be correlated with response using Wilcoxon tests. We will also compare the first 20 patients to the rest in terms of biopsy results using the Fisher test.

We expect to complete study accrual over a 2-3 year time period between MSKCC and Columbia sites, at a rate of 1-2 participants per month.

11. INVESTIGATOR REQUIREMENTS

11.1 Retention of Records

FDA regulations (21 CFR §312.62[c]) and the ICH Guideline for GCP (see Section 4.9 of the guideline) require that records and documents pertaining to the conduct of clinical trials and the distribution of investigational drug, subject records, consent forms, laboratory test results, and medication inventory records, must be retained for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of the investigational product. All state and local laws for retention of records also apply.

11.2 Study Medical Monitoring

This clinical research study will be monitored both by the Sponsor Principal Investigator and by the MSK IRB. The Sponsor Principal Investigator will monitor and review AEs. Appropriate

reporting to the MSK IRB will be made. The Sponsor Principal Investigator of this study will also monitor the conduct, data, and safety of this study to ensure that:

- Stopping rules for toxicity and/or response are evaluated,
- Risk/benefit ratio is not altered to the detriment of the subjects,
- Appropriate internal monitoring of AEs and outcomes is done,
- Over-accrual does not occur,
- Under-accrual is addressed with appropriate amendments or actions, and
- Data are being appropriately collected in a reasonably timely manner.

Routine monitoring will be carried out via a periodic team conference among investigators during which toxicity data, including all SAEs, will be reviewed and other issues relevant to the study such as interim assessment of accrual, outcome, and compliance with study guidelines, will be discussed. Monitoring will be carried out on an ongoing basis. The severity, relatedness, and whether or not the event is expected will be reviewed.

11.3 Study Medication Accountability

The Sponsor Principal Investigator of the study will ensure maintenance of complete and accurate records of the receipt, dispensation, and disposal or return of all study drug in accordance with 21 Code of Federal Regulations (CFR), Part 312.57 and 312.62 and Genentech requirements.
All unused remaining product at the end of the study should be disposed of at the study site according to institutional standard operating procedure. If there is no SOP at the site for drug destruction, return study drug with the Inventory of Returned Clinical Material form.

11.4 Data Collection

The study coordinator and investigators are responsible for ensuring that the eligibility checklist is completed in a legible and timely manner for every subject enrolled in the study, and that data are recorded on the appropriate forms and in a timely manner. Any errors on source data should be lined through, but not obliterated, with the correction inserted, initialed, and dated by the study coordinator or Sponsor Principal Investigator. All source documents will be available for inspection by the FDA and the MSK.

12. ETHICAL CONSIDERATIONS

12.1 Compliance with Laws and Regulations

Subjects who comply with the requirements of the protocol, are tolerating study treatment, and may be receiving benefit will be offered dosing beyond Cycle 1 at the investigator's discretion after a careful assessment and thorough discussion of the potential risks and benefits of continued treatment with the subject. Such subjects may have the option to receive study treatment as long as they continue to experience clinical benefit in the opinion of the investigator until the earlier of unacceptable toxicity, symptomatic deterioration attributed to disease progression, or any of the other reasons for treatment discontinuation listed in Section 5.4.

12.2 Informed Consent

The informed consent document must be signed by the subject or the subject's legally authorized representative before his or her participation in the study. The case history for each subject shall document that informed consent was obtained prior to participation in the study. A copy of the informed consent document must be provided to the subject or the subject's legally authorized representative. If applicable, it will be provided in a certified translation of the local language.

Signed consent forms must remain in each subject's study file and must be available for verification by study monitors at any time.

12.3 Institutional Review Board

This protocol, the informed consent document, and relevant supporting information must be submitted to the IRB for review and must be approved before the study is initiated. The study will be conducted in accordance with FDA, applicable national and local health authorities, and IRB requirements.

The Sponsor Principal Investigator is responsible for keeping the IRB apprised of the progress of the study and of any changes made to the protocol as deemed appropriate.

Investigators are required to promptly notify their respective IRB of all adverse drug reactions that are both serious and unexpected according to institutional policy. Investigators should forward to their IRB any written safety report or update provided by Genentech (e.g., IND safety report, Investigator's Brochure, safety amendments and updates, etc.) according to institutional policy.

12.4 Confidentiality

Subject medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the ICF (or separate authorization to use and disclose personal health information) signed by the subject or unless permitted or required by law.

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

Data generated by this study must be available for inspection upon request by representatives of the FDA and other regulatory agencies, national and local health authorities, Genentech representatives and collaborators, and the IRB/Ethics Committee (EC) for each study site, if appropriate.

12.5 Terminating or Modifying the Study

Adverse event and laboratory data from this trial will be assessed by the Sponsor Principal Investigator on an ongoing basis. SAEs will be reviewed as they are reported to the lead site/sponsor and the PCCTC, and the Sponsor Principal Investigator will make an assessment regarding the safety of continuing or modifying the study. This assessment will be shared with the investigators either in writing or as part of a teleconference. Should the assessment of either the lead site/sponsor or the Sponsor Principal Investigator be that the study should be terminated, the study will be closed to further accrual. Subjects who are receiving study therapy will be assessed individually by the investigator to see if it is in the subjects' best interest to continue, which might be the case for a subject that is responding to the intervention. Follow-up safety assessments will be performed for all subjects who are terminated from the study prematurely.

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APPENDIX A: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	**Description**	**%**	**Description**
0	Normal activity. Fully active, able to continue all prediseaseperformance without restriction.	100	Normal, no complaints, no evidence of disease
		90	Able to carry on normal activity, minor signs or symptoms of disease
1	Symptoms, but ambulatory. Restricted in physically strenuous activitybut ambulatory and able to carryout work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort, some signs or symptoms of disease
		70	Cares for self, unable to carry on normal activity or to do active work
2	In bed < 50% of the time. Ambulatoryand capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requiresoccasional assistance but is able to care for most needs
		50	Requiresconsiderable assistance and frequent medical care
3	In bed > 50% of the time. Capable of only limited self-care, confinedto bed or chair > 50% of waking hours.	40	Disabled, requires special care and assistance
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled, cannot carry on any self-care, totally confinedto bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly
5	Dead	0	Dead

APPENDIX B: STUDY CALENDAR

Assessments (Cycle length = 21 days)	Screening	Treatment/Intervention Period [l]								End of Treatment [l]	Follow Up
		Cycle 1		Cycle 2		Cycle 3	Cycle 4	Cycle 5	Cycle 6+		
	Day -30 to Day -1	Day 1 (±3 d)	Day 14	Day 1 (±3 d)	Day 10-15	Day 1 (±3 d)	Day 1 (±3 d)	Day 1 (±3 d)	Day 1 (±3 d)	Within 30 days of last dose	Every 6 Months (±4 weeks)
Informed consent and research authorization/ HIPAA form [a]	X										
Demographics, medical history, histologic confirmationof disease	X										
Concomitant medications	X	X		X		X	X	X	X	X	
Adverse Events				X							
Vitals (Blood Pressure, Pulse, Temperatureand weight)	X	X		X		X	X	X	X	X	
Performance status [b]	X	X		X		X	X	X	X	X	
Physical Examination	X	X		X		X	X	X	X	X	
Laboratory tests [c]	X	X		X		X	X	X	X	X	
AST/ALT/Total Bilirubin [d]	X	X		X		X	X	X	X		
ECG	X										
MR Prostate/Pelvis [e]	X										
CT chest/abdomen/pelvis or CT Chest and MR abdomen/pelvis [e]	X			*8 weeks from C1D1 and then every 8 weeks from the date of the subject's previous scan (+/- 4 weeks) for 1st year and then every 12 weeks (+/- 4 weeks) until end of treatment.*							
Bone Scan [e]	X			*8 weeks from C1D1 and then every 8 weeks from the date of the subject's previous scan (+/-4 weeks) for 1st year and then every 12 weeks (+/- 4 weeks) until end of treatment.*							
PCWG3 and RECIST Tumor measurements	X			*Tumor measurements will be repeated with each imaging timepoint. Imaging will also be reviewed for significant sigmoid diverticulosis at screening.*							
Prostate Biopsy [f]	X		X			X					
Metastatic Biopsy [g]	(X)									X	
Correlative Blood Draws [h]		X		X			X		X	X	
Normal control blooddraw [h]		X									
Atezolizumab Administration [i]		X		X		X	X	X	X		

Assessments (Cycle length = 21 days)	Screening	Treatment/Intervention Period [l]								End of Treatment [l]	Follow Up
		Cycle 1		Cycle 2		Cycle 3	Cycle 4	Cycle 5	Cycle 6+		
	Day -30 to Day -1	Day 1 (±3 d)	Day 14	Day 1 (±3 d)	Day 10-15	Day 1 (±3 d)	Day 1 (±3 d)	Day 1 (±3 d)	Day 1 (±3 d)	Within 30 days of last dose	Every 6 Months (±4 weeks)
Abiraterone/Prednisone Administration [l] (Subjects enrolled prior to Protocol V4)				X							
Enzalutamide Administration [l] (Subjects enrolledon Protocol V4)				X							
GnRH Administration [i]						X					
Fiducial Marker Placement [i]			X			X					
Radiation [j]					X						
Stereotactic Body Radiotherapy								X			
Post-Treatment Subsequent Cancer Therapy and Progression Status (Clinical, PSA or Radiographic Progression) [m]											X
Survival Status [k]											X

FOOTNOTES:

a. Informed consent shouldbe obtainedwithin 30 days of treatment start.

b. Performance status will be assessed using the ECOG scale

c. Laboratory tests will be performedand will include: CBC with differential: white bloodcells count (WBC), redbloodcell count (RBC), hemoglobin (HGB), hematocrit (HCT), platelet count (UNVPLT), neutrophils (NEUTP), lymphocytes(LYMP), monocytes (MONP), eosinophils (EOSP), basophils (BASOP)); Comprehensive Metabolic Panel: (glucose (GLU), calcium (CA), albumin (ALB), total protein(TP), sodium (NA), potassium (K), bicarbonate (CO2), chloride (CL), blood urea nitrogen (BUN), creatinine (CREAT), alkaline phosphatase (ALK), alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin (TBILI), magnesium (MG); PSA; serum testosterone/dihydrotesterone (TEST); amylase; lipase; TSH; Free T4; C-Reactive Protein (CRP); Hepatitis B and C, and HIV Serology. Serum testosterone will be collected on Day 1 of each cycle through Cycle 6. PTT/PT and INR, Hepatitis B (HBsAg and HBV PCR) and Hepatitis C, HIV Serology, and CRP are required at screening only. Some labs may require to be drawn for eligibility within 14 days of treatment start. Please refer to inclusion 3.1.7 for a list of these labs):

d. AST, ALT and total bilirubin should be monitoredfrom C1D1 (C1D1, C1D15, C2D8, C3D1, C3D15, C4D8 for abiraterone-treated subjects) and thenon Day 1 of each cycle thereafter (enzalutamide-treated subjects only required LFTs to be monitoredon D1 or D-1 of each cycle). Labs may be drawn at an outside facility. Starting treatment on C1D1 should not be held if LFTs have not resultedin time.

e. Radiographic evaluations includingCT chest/abdomen/pelvis, preferably with contrast or MRI abdomen/pelviswith CT chest; dedicated MRI of the prostate; Technetium-99 Whole Body Bone Scan; MR of the prostate may be obtainedup to 90 days prior to treatment start and is required at screening only. Radiologic documentation will be provided for subjects removedfrom study for progressive disease.

f. Subjects will undergoan up-front prostate biopsy per standard of care prior to treatment initiation. Archival tissue from the subject's initial prostate biopsy may be acceptedin lieu of a new prostate biopsyif adequate tissue is available. Verbal confirmationof sufficient prostate biopsymaterial for genomic profiling testing must be confirmedbefore confirmation of eligibility. Subjects will also undergo one on-treatment prostate researchbiopsy:

For first 20 subjects: a visually targeted, MR guided, multi-core prostate biopsy of the dominant lesion must occur between Cycle 1 Day 14 and Cycle 2 Day 3

For remaining subjects: a visually targeted, MR guided, multi-core prostate biopsyof the dominant lesionmust occur between Cycle 3 Day 1 and Cycle 3 Day 14

g. In addition to prostate tumor tissue, collection of tissue from a metastatic site of disease is optional if subject has undergone or will be undergoing a baseline standard of care biopsy of a metastatic site. A metastatic tissue biopsy at progression of disease 21 days after discontinuation of treatment is required if safe and feasible.

h. Blood for T cell and MDSC flow cytometry, TCR sequencing, CyTOF and ctDNA will be collected on Day 1 of Cycles 1, 2 4, and 6, and upon progression of disease at the End of Treatment visit. Baseline blooddraw for correlatives should be drawn prior to treatment start on C1D1. Collection, processing and shipment instructionscan be found in the laboratory manual.

- For CUMC subjects ONLY: a whole blood sample will be collected for a genetic profiling test normal control prior to treatment start on C1D1.

i. Cohort 1: First 20 subjects enrolled, unless on hormone therapyprior to treatment start:

- Atezolizumab will be administered on Cycle 1 Day 1 and thenevery 21 days (±3 days) from the date of the subject's previous atezolizumab administration. Atezolizumabwill be heldfor cycles 6 and 7 post SBRT. Patients will restart after repeat imaging at Cycle 8.
- Fiducial marker placement will occur between Cycle 1 Day 14 and Cycle 2 Day 3. Fiducial marker placement will include a visually targeted, MR guided, multi-core biopsy of the dominant lesion as described in footnote f.
- Abiraterone/prednisone will be initiated within 1-14 days after fiducial placement for subjects enrolled prior to protocol version 4
- Enzalutamide will be initiated within 1-14 days after fiducialplacement for subjects enrolledafter protocol version 4
- GnRH analog will be initiated Cycle 3 Day 1 ± 5 days then at a dose and frequencysuggestedby the drug manufacturers instructions.

Cohort 2: Remaining patients after 20 first subjects and/or subjects on prior hormone therapy:

- Atezolizumab will be administered on Cycle 1 Day 1 and thenevery 21 days (±3 days) from the date of the subject's previous atezolizumab administration. Atezolizumabwill be heldfor cycles 6 and 7 post SBRT. Patients will restart after repeat imaging at Cycle 8.
- Abiraterone/prednisone will be initiated at Cycle 2 Day 1 (±7 days) after fiducialplacement for subjects enrolledprior to protocol version 4
- Enzalutamide will be initiated at Cycle 2 Day 1 (±7 days) after fiducial placement for subjects enrolled after protocol version 4
- Fiducial marker placement will occur between Cycle 3 Day 1 and Cycle 3 Day 14. Fiducial marker placement will include a visually targeted, MR guided, multi-core biopsy of the dominant lesion as described in footnote f.
- GnRH analog will be initiated after fiducial placement. This can be same day or any time up to and including C4D1 at a dose and frequency suggested by the drug manufacturers instructions. For subjects on hormonal therapyprior to treatment start, continue GnRHas prescribed.

j. Radiation simulation shouldoccur within 28 days before SBRT

k. Survival Status will be collected via telephone calls, subject medical records, and/or clinic visits every 6 months (+/- 4 weeks) until death, lost to follow-up, withdrawal of consent (documented in medicalrecord) or study termination. All subjects will be followed for survival and new anti-cancer therapy (including systemic, surgical and radiotherapy) and secondary and exploratory efficacyendpoints unless the subject requests to be withdrawn from follow-up; this request must be documentedin the source documents and signed by the investigator.

l. Telemedicine and local assessments canbe completedas necessary. Physical exams will be waived for telemedicine visits and not require a deviation to be completed. Correlative blood draws cannot be waived or done locallyand will needto be arrangedto be completed onsite.

m. Subjects who discontinue study treatment for reasons other than progressionwill be followedevery 6 months (+/- 4 weeks) until a documented progression event (i.e., PSA, radiographic, or clinical progression).

APPENDIX C: MEDICATIONS WITH THE POTENTIAL FOR DRUG-DRUG INTERACTIONS-ABIRATERONE

Concomitant use of medications that may alter pharmacokinetics of abiraterone will not be allowed on this study. Specifically, strong CYP3A4 inhibitors or inducers that decrease the exposure of abiraterone will not be allowed.

Strong CYP3A4 Inducers	Strong CYP3A4 Inhibitors
Aminoglutethimide	Atazanavir
Bexarotene	Clarithromycin
Bosentan	Delavirdine
Carbamazepine	Diltiazem
Dexamethasone	Erythromycin
Efavirenz	Indinavir
Fosphenytoin	Itraconazole
Griseofulvin	Nefazodone
Modafinil	Nelfinavir
Nafcillin	Ritonavir
Nevirapine	Saquinavir
Oxcarbazepine	Telithromycin
Phenobarbital	Verapamil
Phenytoin	Voriconazole
Primidone	Grapefruit juice (or grapefruits)
Rifabutin	
Rifampin	
Rifapentine	
Tipranavir	
St. John's wort	

APPENDIX D: MEDICATIONS WITH THE POTENTIAL FOR DRUG-DRUG INTERACTIONS-ENZALUTAMIDE

Enzalutamide is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer in humans [Xtandi® Prescribing Information] and may decreasethe exposure of comedications that are substrates for these metabolizing enzymes.

Strong Inhibitors	**Strong Inducers**
Indinavir	Carbamazepine
Nelfinavir	Phenobarbital
Ritonavir	Phenytoin
Clarithromycin	Rifabutin
Itraconazole	St. John's wort
Ketoconazole	Troglitazone
Nefazodone	Secobarbital
Fluconazole	Rifampin
Telithromycin	
Fluvoxamine	
Mibefradil	
Omeprazole	
Ticlopidine	
Fruit and juice:	
Star fruit	
Pomegranate	
Grapefruit	
Seville oranges	
Papaya	

APPENDIX E: GLOSSARY OF ABBREVIATIONS AND ACRONYMS

AA	abiraterone acetate
ADT	androgen deprivation therapy
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the concentration curve
CODP	chronic obstructive pulmonary disease
CT	computed tomography
CTAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
CyTOF	mass cytometry
EC	ethics committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EtMs	events to monitor
FDA	US Food and Drug Administration
FFS	failure-free survival
GCP	Good Clinical Practice
GnRH	gonadotropin-releasing hormone
HIPAA	Health Insurance Portability and Accountability Act of 1996
I.B.	investigator brochure
IC	immune cells
ICB	immune checkpoint blockade
ICF	informed consent form
Ig	immunoglobulin
IHC	Immunohistochemistry
IL-2	interleukin 2
IMP	investigational medicinal product
IMPACT	Integrated Mutation Profiling of Actionable Cancer Targets
IRB	institutional review board
IRR	infusion related reaction
IV	intravenous
mCRPC	metastatic castration-resistant prostate cancer
mHSPC	metastatic hormone-sensitive prostate cancer
MDSC	myeloid-derived suppressor cell
MRC	Medical Research Council
MSK	Memorial Sloan Kettering Cancer Center
mUC	metastatic urothelial carcinoma

NCI	National Cancer Institute
NSCLC	non-small cell lung cancer
OS	overall survival
P.I.	package insert
PCCTC	Prostate Cancer Clinical Trials Consortium
PCWG3	Prostate Cancer Working Group 3
PD-L1	programmed death-ligand 1
PSA	prostate-specific antigen
QOL	quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	severe adverse event
SBRT	stereotactic body radiotherapy
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SRE	skeletal-related event
STIAMP	suspected transmission of an infectious agent via a medicinal product
TCR	T cell receptor
TMB	tumor mutation burden
ULN	upper limits of normal

APPENDIX F: DEFINITION OF BIOMCHEMICAL FAILURE

Biochemical failure: The initial response to hormonal therapy for prostate cancer can be variable. A few patients exhibit only a small fall in PSA, with little evidence of clinical response. At the other extreme a rapid fall to the normal range or even undetectable levels of PSA occurs. In a group of patients the response lies between these two extremes. The rate of fall of PSA and the level of the PSA nadir are recognized to have prognostic significance. Comparison of PSA responses between the treatment groups could be used as secondary data for confirming the response rate of the trial treatments. However, in defining PSA relapse, the extent of the primary response has to be taken into account. Three groups of subjects will be defined:

A. If the PSA nadir is more than 50% of the last pre-treatment PSA, the subject should be defined as a treatment failure (at time zero).

B. For subjects whose PSA falls by more than 50% of the last pre-treatment PSA, but remains above 4ng/ml, PSA relapse will be deemed to have occurred when PSA is confirmed as increasing by 50% above the nadir level.

C. For subjects whose PSA falls below 4ng/ml, PSA relapse will be defined by either 50% increase from their nadir or the PSA increasing above 4, whichever is the greater. For example, a nadir PSA of 3.6 would require a PSA of 5.4 to define relapse, while PSA nadir of 2.5 will be considered to have relapsed at a PSA of 4.

Timing of PSA tests: The final pre-treatment PSA must be measured within 4 weeks prior to treatment start. Once on trial, PSA tests will be performed at the beginning of every cycle (e.g. every 3 weeks)

Nadir PSA: The PSA nadir will be the lowest reported PSA level between treatment start and the beginning of cycle 8. The critical value that would constitute subsequent biochemical progression will be calculated from this nadir value.

Confirming failure-free survival (including biochemical failure): Any isolated PSA rise should be confirmed before reporting biochemical failure. In the case that the raised PSA value reaches the progression value, a confirmatory PSA test should be performed at the next cycle start. Biochemical failure is confirmed if the second value is around the same level or higher (i.e. the trend is confirmed).