DF/HCC Protocol #: *20-701*

TITLE: A Phase II Multi-Center Trial of Abemaciclib with or without Atezolizumab in Metastatic Castration Resistant Prostate Cancer

Sponsor-Investigator: **Atish Choudhury, MD PhD**
Dana-Farber Cancer Institute
450 Brookline Ave, Dana 930
Boston, MA 02215
Phone: (617) 632-6328
Fax: (617) 632-2165
Email: achoudhury@partners.org

Co-Investigators:

Zachery Reichert, MD
University of Michigan
Email: zreiche@med.umich.edu

Aihua Yen, MD
Baylor College of Medicine
E-mail: ay044661@bcm.edu

Melissa Reimers, MD
Washington University
E-mail: mreimers@wustl.edu

David Einstein, MD
Beth Israel Deaconess Medical Center
E-mail: deinstei@bidmc.harvard.edu

Statistician: Lucia Kwak, MS
Dana-Farber Cancer Institute
Email: lkwak@ds.dfci.harvard.edu

Supplied Agents: Abemaciclib, Eli Lilly; Atezolizumab, Genentech

IND Exempt
IND Sponsor: *Atish Choudhury, MD PhD*

Protocol Type / Version # / Version Date: *Version 8: 08/15/2023*

ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
ALC	Absolute Lymphocyte Count
AST	Aspartate Aminotransferase
BID	Twice (two times) a Day
BUN	Blood Urea Nitrogen
CBCD	Complete Blood Count with Differential
CLIA	Clinical Laboratory Improvement Amendments
CMP	Comprehensive Metabolic Panel
CPI	Checkpoint Inhibitor Immunotherapy
CPK	Creatinine Phosphokinase
CR	Complete Response
CRS	Cytokine Release Syndrome
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTSU	Clinical Trials Support Unit
DLCO	Diffusing capacity of the Lungs for Carbon Monoxide
DLT	Dose Limiting Toxicity
DSMC	Data and Safety Monitoring Committee
ECMO	Extracorporeal Membrane Oxygenation
FEV1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
GGT	Gamma-glutamyl Transferase
HLH	Hemophagocytic lymphohistiocytosis
H&P	History & Physical Exam
HRPP	Human Research Protections Program
HRR	Homologous Recombination Repair
Ig	Immunoglobulin
IND	Investigational New Drug
INR	International Normalized Ratio
irAE	Immune-related Adverse Event
IRB	Institutional Review Board
irPD	Immune-related Progressive Disease
IRR	Infusion-Related Reaction
IV (or iv)	Intravenously
LFTs	Liver Function Tests
LLN	Lower Limit of Normal
MAS	Macrophage activation syndrome
MTD	Maximum Tolerated Dose

mCRPC	Metastatic castration resistant prostate cancer
NCI	National Cancer Institute
ORR	Objective Response Rate
OS	Overall Survival
PBMCs	Peripheral Blood Mononuclear Cells
PD	Progressive Disease
PFS	Progression Free Survival
PFT	Pulmonary Function Test
PI	Principal Investigator
P.O.	per os/by mouth/orally
PR	Partial Response
PRC	Protocol Review Committee
pts	Patients
RBC	Red Blood Cell count
SAE	Serious Adverse Event
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SPGT	Serum Glutamic Pyruvic Transaminase
STIAMP	Suspected transmission of an infectious agent
UaP	Unanticipated Problem
ULN	Upper Limit of Normal
VAD	Ventricular Assist Device
WBC	White Blood Cells
ULN	Upper Limit of Normal

SUMMARY OF CHANGES

Protocol changes

Section	Change
Title Page	Updated version number and date. Changed Baylor College of Medicine PI from Arpit Rao to Aihua Yen
Abbreviations	Added "pts" = Patients
Schema, Synopsis, 1.1, 5	Updated study design to account for closure of Arm B and combination cohort of Arm C to further enrollment. Updated study design for Arm C such that after the exploratory cohort of 5 patients treated with atezolizumab are enrolled, the subsequent 16 patients will be treated with abemaciclib monotherapy rather than abemaciclib with atezolizumab.
Synopsis, 1.4, 13.1.3, 13.5	Updated primary biomarker objective and statistical plan to note that "the FoxP3+/CD8+ T-cell ratio in all biopsy specimens and the change between pre-treatment and on-treatment specimens will be reported descriptively for each treatment arm separately" rather than comparing monotherapy to combination therapy.
Synopsis, 13.2	Updated sample size for Arms A and B from 27 in each arm to 27 in Arm A and 8 in Arm B (i.e. from 54 to 35 total across Arms A and B) and for the total trial from 75 to 56 patients
Synopsis, 1.1, 5	Removed Arm B and combination cohort for Arm C from Treatment Plan and added abemaciclib monotherapy for 16 patients in Arm C.
Synopsis, 3.3.27	Added exclusion criterion for treatment with systemic immunosuppressive medication
Synopsis, 13.2	Updated efficacy analysis as follows: • Removed efficacy analysis and sample size justification for Arm B, and instead noted "The efficacy endpoints of 6m-PFS and ORR in patients treated with combination of abemaciclib and atezolizumab in arm B will be listed individually due to small number." • Updated efficacy analysis for Arm C to reflect 16 patients treated with abemaciclib monotherapy rather than abemaciclib with atezolizumab
Synopsis, 1.1, 13.3	Updated the safety analysis to note: "Due to two grade 5 sepsis events observed in the 8 patients treated on Arm B with unclear relationship to the study medications, the Sponsor-Investigator and co-investigators elected to halt enrollment to combination treatment rather than following the Bayesian toxicity monitoring plan" and modified the analysis plan accordingly
Synopsis, 1.1, 13.3, Table 28, Table 29	Clarified the Bayesian toxicity monitoring plan such that de-escalation and stopping rules are based on the number of patients experiencing DLT rather than the total number of DLTs.
1.3	Added arm names for clarification

2.2	Updated FDA approvals for atezolizumab
6.1	Added general recommendations for management of any other adverse events related to atezolizumab that may occur and are not specifically listed Added to Pulmonary Event, Grade 3 or 4: "Oral or IV broad-spectrum antibiotics should be administered in parallel to the immunosuppressive treatment." Added to Diarrhea or colitis, Grade 2 or 3: "If the event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent." Updated language and management guidelines for endocrine events, cardiac events, neurologic disorders, per most current atezolizumab template. Added to Hemophagocytic lymphohistiocytosis and macrophage activation syndrome: "Clinical and laboratory features of severe CRS overlap with HLH, and HLH should be considered when CRS presentation is atypical or prolonged."
7.1.2	Added facial paresis and myelitis as expected toxicities of atezolizumab, changed "pericarditis" to "pericardial disorders."
7.2.2	Added "i.e., the AE results in substantial disruption of the **subject's ability to conduct normal life functions**" that was missing in error
7.2.8	Added facial paresis and myelitis as adverse events of special interest with atezolizumab
7.4	Adverse event reporting requirements clarified
7.6	Added MedWatch 3500A Reporting Guidelines to Reporting Procedures to Genentech
7.6.1	In Case Transmission Verification of Single Case Reports, added information regarding Reporting to Regulatory Authorities, Ethics Committees and Investigators
8.1.4	Added "In the event a subject cannot be seen for a cycle visit due to COVID-19 infection or suspicion for COVID-19 infection, abemaciclib may be shipped upon approval of PI."
9.1.2	Added "The window for the on-treatment biopsy can be extended per PI discretion if the patient required dose interruption(s) prior to the biopsy."
11.1.4	Replaced "Cohorts B and C" with "Patients receiving Atezolizumab"
13.1.1, 13.3	Corrected erroneous reference to DLT definition from section 7.4 to section 7.3.

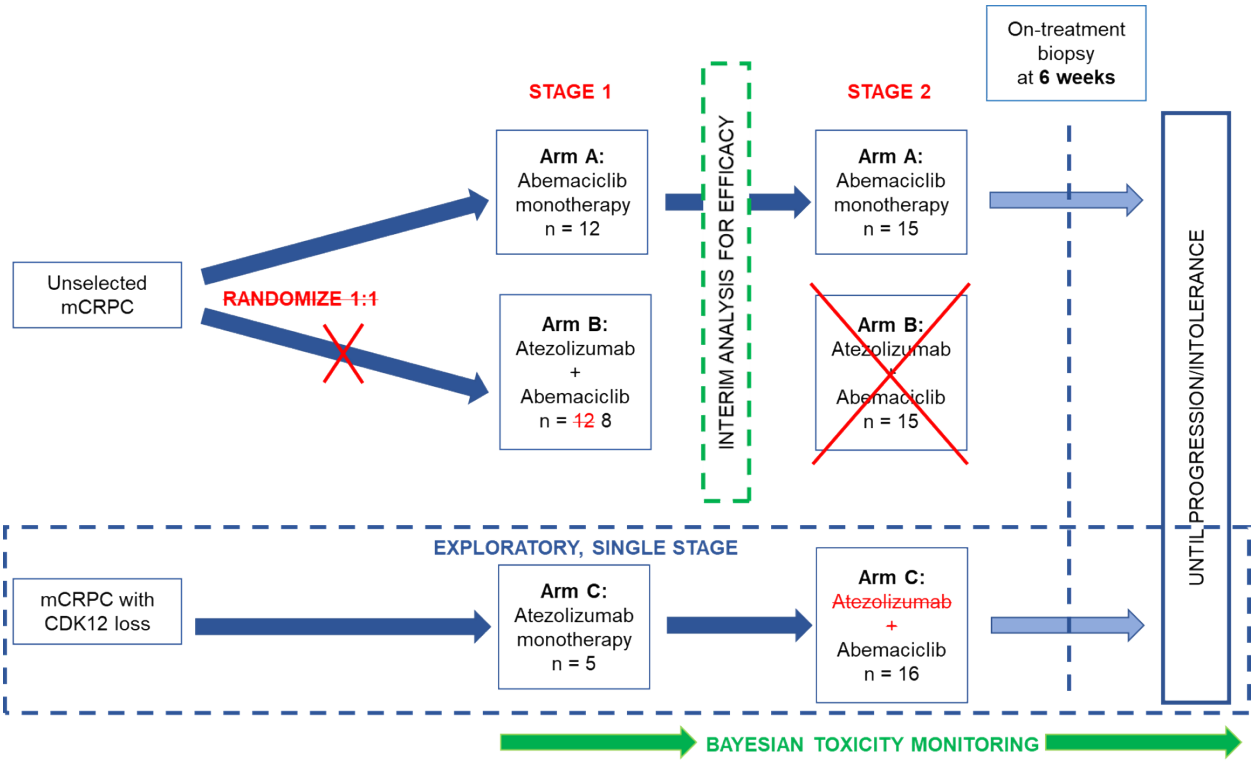
13.3, Table 28	Clarified that patients must have received at least 28 days of trial therapy (or have experienced a DLT) to be considered DLT-evaluable.
Appendix E	Added autoimmune myelitis to the list of Autoimmune Diseases and Immune Deficiencies

Informed Consent Form changes

Section	**Change**
2	Edited to include note that the combination of atezolizumab and abemaciclib is no longer being studied
4	Removed reference to combination. Updated new total enrollment number from 75 to 56.
A. Why is this Research Study Being done	Edited to include note that the combination of atezolizumab and abemaciclib is no longer being studied, and added rationale for atezolizumab monotherapy and abemaciclib monotherapy in patients with *CDK12* mutations as follows: • "Atezolizumab is ineffective on its own in most patients with prostate cancer, but **may be effective in certain subsets of patients and** is being tested in combination with other drugs for prostate cancer in other clinical trials." • "There are other studies that have demonstrated that cancers with mutations in the CDK12 gene often have other genetic changes that may lead them to be sensitive to cyclin dependent kinase inhibitors, so we are also testing whether abemaciclib is effective in these patients."
B. What is involved in this Research Study?	Removed information about randomization. Removed information about arm B and the combination treatment information for arm C due to cohort closures.
C. What are the risks or discomforts of the research study?	Added the following to risks associated with abemaciclib: "**Rare** (Less than a 1% chance that this will happen) • Fever with decreased number of white blood cells in the blood (neutropenia) has been reported in less than 1% of patients exposed to abemaciclib across trials. This can lead to severe generalized infection (sepsis) with side effects involving several organs in your body (for example, liver, kidney, lungs, and bone marrow), causing a serious condition, which could lead to hospitalization, life-threatening circumstances, or even death. Two deaths due to neutropenic sepsis were observed in a study of abemaciclib called MONARCH 2."
C. What are the risks or discomforts of the research	Added the following to risks associated with atezolizumab: "Abemaciclib may be an immune-modulating drug that when combined with atezolizumab could increase the risk of sepsis resulting in death, so the combination of atezolizumab with abemaciclib is no longer being studied."

study?	

SCHEMA



SYNOPSIS

Title	A Phase II Trial of Abemaciclib with or without Atezolizumab in Metastatic Castration Resistant Prostate Cancer
Phase	Phase II
Methodology	Open-label
Study Duration	36 months
Study Center(s)	Multi-Center: up to 5 sites including lead site: Dana-Farber Cancer Institute
Objectives	Primary Objectives: 1. To determine the efficacy of abemaciclib monotherapy in biomarker-unselected patients with metastatic CRPC (Arm A). 2. To determine the efficacy of abemaciclib in combination with atezolizumab in biomarker-unselected patients with metastatic CRPC (Arm B). 3. To determine the safety of abemaciclib in combination with atezolizumab in mCRPC (Arm B).

	Secondary Objectives: 1. To evaluate secondary measures of clinical efficacy of abemaciclib monotherapy (Arm A) and abemaciclib in combination with atezolizumab (Arm B)in biomarker-unselected cohort. 2. To identify the clinical variables associated with response and resistance to therapy including type of prior antiandrogen therapy (CYP17 inhibitor or AR antagonist), duration since prior antiandrogen therapy, receipt of prior chemotherapy, and visceral- versus bone- predominant disease (Arms A and B). 3. To determine the safety and adverse event profiles of abemaciclib monotherapy and abemaciclib in combination with atezolizumab in mCRPC (all Arms). Exploratory/Translational Objectives: 1. To assess the efficacy of atezolizumab alone and abemaciclib monotherapy in the CDK12 loss cohort (Arm C). 2. Primary translational objective: To assess FoxP3+/CD8+ ratio in all biopsy specimens and the change between pre-treatment and on-treatment specimens will be reported descriptively for each treatment arm separately). 3. To perform detailed profiling of tumor immune infiltrate from paired baseline (where available) and on-treatment tumor biopsies in biomarker-unselected and CDK12 mutant cohorts (all Arms). 4. Evaluate changes in androgen-receptor signaling pathway with exposure to abemaciclib monotherapy and abemaciclib in combination with atezolizumab (all Arms). 5. Identify the biomarkers of response and resistance to abemaciclib monotherapy and in combination with atezolizumab in biomarker-unselected patients (Arm A and B).
Number of Subjects	Arms A and B: 35 total (27 in Arm A and 8 in Arm B) Arm C: 21 total Total trial: 56 patients
Inclusion Criteria	(All patients) 1 Diagnosis of metastatic castration resistant prostate cancer (mCRPC), with histologic confirmation of adenocarcinoma of the prostate, without evidence of small cell carcinoma. 2 Adult males 18 years of age or older. 3 ECOG performance status of 0 or 1. 4 Presence of a lesion (bone or soft tissue) amenable to image-guided percutaneous biopsy, and patient evaluable for response based on: baseline PSA ≥ 2 ng/mL OR measurable disease per RECIST 1.1 criteria. 5 Past progression or intolerance to at least one novel antiandrogen therapy (abiraterone, enzalutamide, galeterone, apalutamide, darolutamide, orteronel, seviteronel or equivalent) in either the hormone-sensitive or castration-resistant disease setting. 6 Not a candidate for docetaxel or cabazitaxel chemotherapy due to:

	progression within 12 months of completion or intolerance to prior taxane OR refusal of taxane OR contraindication to, or lack of fitness for taxane OR Investigator assessment that taxane is not clinically indicated or preferred. 7 Maintenance of castration status, defined as serum testosterone level of less than 50 ng/dL. Patients must be surgically castrate or maintained on LHRH agonist or antagonist therapy for the duration of the study period. 8 Must have recovered from any treatment-related toxicities to ≤ CTCAE grade 1. *Patients with ≤ CTCAE grade 2 anorexia, alopecia, neuropathy, and/or fatigue however, are also permitted to enroll.* 9 Patients must have normal organ and marrow function as defined below: -leukocytes ≥3,000/mcL -absolute neutrophil count ≥1,500/mcL -lymphocyte count ≥500/mcL -hemoglobin ≥9 g/dL (without transfusion or growth factor in prior 28 days, except for patients assigned to atezolizumab monotherapy in Arm C for whom transfusion to meet this eligibility criterion is permitted) -platelets ≥100,000/mcL (without transfusion or growth factor in prior 28 days) -serum albumin ≥ 25 g/L (2.5 g/dL) -total bilirubin ≤1.5 × institutional upper limit of normal, unless the subject has known or suspected Gilbert's syndrome in which case total bilirubin must be ≤ 2 × ULN -AST(SGOT)/ALT(SGPT) ≤1.5 × institutional upper limit of normal, except for patients assigned to atezolizumab monotherapy in Arm C for whom ≤2.5 × upper limit of normal is permitted -INR and aPTT ≤1.5 × institutional upper limit of normal, unless the subject is receiving therapeutic anticoagulation, in which case they must be on a stable anticoagulant regimen -creatinine clearance ≥30 mL/min/1.73 m2 10 Life expectancy of at least 6 months, as determined by a study Investigator. 11 Ability to swallow oral medications. 12 Ability to understand and willingness to sign an IRB-approved informed consent. (Arm C patients, additional criterion) 1 Must have documentation (via CLIA approved, CAP certified next generation sequencing [NGS] assay report) of genomic aberration resulting in CDK12 loss of function in metastatic tumor tissue.
Exclusion Criteria	(All patients) 1 History of leptomeningeal disease, or clinical evidence of, or known and untreated metastatic CNS disease.

	2 Concurrent active malignancy with the exception of malignancies with a negligible risk of metastasis or death (e.g., 5-year OS rate > 90%). *Patients with adequately treated non-melanomatous skin cancer, cancer not needing active therapy for at least 2 years, cancer for which the treating investigator deems the subject to be in remission, or any prior malignancy that was treated with curative intent (no evidence of disease for at least 3 years) are also permitted to enroll.* 3 Treatment with chemotherapy or radiotherapy within 4 weeks prior to planned cycle 1 day 1 of study treatment. 4 Treatment with investigational therapy within 28 days prior to initiation of study treatment. 5 Treatment with oral anti-neoplastic intervention such as an oral hormonal agent, PARP inhibitor, or AR targeted therapy within 14 days prior to planned cycle 1 day 1 of study treatment. 6 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. 7 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. 8 Prior treatment with an inhibitor of CDK4 and/or 6. 9 Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti– CTLA-4, anti–PD-1, PD-L1, or PD-L2 therapeutic antibodies. 10 History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins. 11 Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab formulation. 12 Known allergy or hypersensitivity to any component of the abemaciclib formulation. 13 Patients on concurrent therapy with a moderate or strong CYP3A4 inducer or inhibitor, which cannot be safely stopped at least five half-lives prior to initiation of therapy with abemaciclib. 14 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 (see Appendix E for a more comprehensive list of autoimmune diseases and immune deficiencies), with the following exceptions: *Patients with a history of autoimmune-related hypothyroidism who are on thyroid-replacement hormone are eligible for the study.* *Patients with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study.* *Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with*

	psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met: *-Rash must cover < 10% of body surface area* *-Disease is well controlled at baseline and requires only low-potency topical corticosteroids* *-There has been 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* 15 Prior allogeneic stem cell or solid organ transplantation 16 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 17 Active smoking (of tobacco, marijuana, or any other substance) or vaping at time of enrollment, or a history of smoking equivalent to greater than 20 pack-years of cigarettes. 18 Prior history of radiation therapy to thorax (including to lungs/pleura, esophagus, intrathoracic lymph nodes, C7-L2 vertebrae, or ribs) for any reason and any duration/dose. This exclusion criterion does not apply to patients assigned to atezolizumab monotherapy in Arm C, who may have received prior radiation to thorax. 19 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. 20 Active tuberculosis 21 Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently) *Patients with indwelling catheters (e.g., PleurX®) are allowed.* 22 Any history of lung cancer, regardless of stage or treatment 23 Any of the following abnormalities on pre-treatment pulmonary function testing: a. FEV1/FVC ratio < lower limit of normal (LLN) and FEV1 < 75% predicted OR b. FVC < 70% of predicted, regardless of FEV1/FVC ratio OR c. DLCO (corrected for hemoglobin) < 70% of predicted 24 Uncontrolled tumor-related pain *Patients requiring pain medication must be on a stable regimen at study entry.* *Symptomatic lesions (e.g., bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated prior to enrollment. Patients should be recovered from the 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. 25 Uncontrolled or symptomatic hypercalcemia (ionized calcium > 1.5 mmol/L, calcium > 12 mg/dL or corrected serum calcium > ULN) 26 Severe infection, or active known detectable viral infection (e.g., Human Immunodeficiency Virus [HIV] or viral hepatitis) within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia, or any active infection that could impact patient safety. 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: *Patients who received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study.* *Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease (COPD) or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study.* 28 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.* 29 Current treatment with anti-viral therapy for HBV. 30 Arterial or venous thromboembolic event within the last 3 months. 31 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 3 months prior to initiation of study treatment. 32 Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications. 33 Significant infection, medical condition, or social situation which, in the opinion of the investigator, would preclude participation or limit the patient's ability to comply with study requirements.
Study Product(s), Dose, Route, Regimen	<u>Arm A:</u> Abemaciclib 200 mg orally BID Days 1-21 <u>Arm C:</u>

	Atezolizumab 1200 mg IV on Day 1 OR Abemaciclib 200 mg orally BID Days 1-21 All cycles are 21 days in length. Starting doses are subject to safety analyses.
Duration of Administration	Patients may be treated until disease progression or unacceptable toxicity or other reasons subject to Investigator/patient discretion.
Statistical Methodology	*Efficacy Analysis* 27 total evaluable patients in Arm A will provide 86% power for 6 month progression-free survival (with null 6m-PFS 12% and alternative of 34%) and 85% power for objective response rate (with null ORR 10% and alternative of 30%) and with a one-sided type 1 error of 8%. When 12 patients in Arm A have been enrolled and followed for maximum 6 months, Arm A will close if there is no patient with response or with 6m-PFS. Otherwise, the 2nd stage will open, and 15 more patients will be enrolled in that arm for 8 months for a total of 27 patients. The 6m-PFS Kaplan-Meier estimate for Arm A will be reported with a 90% confidence interval. If 6 patients experience 6m-PFS or 5 patients have an objective response by the end of stage 2, this study would suggest meaningful clinical activity. For Arm C (CDK12 loss CRPC), similar assumptions will be made with expected efficacy with a null 6m-PFS rate of 12% and an alternative response of 34% or greater with abemaciclib therapy. Due to accrual limitations in this arm, we will use a single stage design. Five patients with CDK12 loss will be accrued to an atezolizumab monotherapy as exploratory group. Then, 16 additional subjects with CDK12 loss will be accrued to therapy with abemaciclib for 18 months, the same accrual time as arm A. A one-sided, one-sample log-rank test calculated from a sample of 16 subjects achieves 80-85% power at a 0.05 significance level to detect 22% of difference in 6m-PFS. Follow-up continues for 12 months after the last subject is added. The 6m-PFS Kaplan-Meier estimate will be reported with a 90% confidence interval. *Safety analysis* Safety and tolerability for abemaciclib monotherapy and for the combination of abemaciclib and atezolizumab will be summarized by rate of dose-limiting toxicities (DLTs) as defined in section 8.3.8 using percentage and 90% confidence interval, and by incidence and grade of adverse events (AEs) by CTCAE version 5.0. Bayesian toxicity monitoring was planned to be used for all patients enrolled to Arm B and to the combination treatment cohort of Arm C (up to a maximum of 43 patients). If the rate of patients experiencing dose limiting toxicities (DLTs) at the starting dose exceeded the pre-specified threshold for excessive toxicity, then subsequent patients randomized to

	Arm B or enrolled to the combination cohort of Arm C were planned to receive abemaciclib at one dose level reduction (100 mg BID) with atezolizumab 1200 mg every 21 days. If the rate of patients experiencing DLTs at the reduced dose exceeded the pre-specified threshold for excessive toxicity, then enrollment to Arm B and the combination cohort of Arm C was planned to be halted. Due to two grade 5 sepsis events observed in the 8 patients treated on Arm B with unclear relationship to the study medications, the Sponsor-Investigator and co-investigators elected to halt enrollment to combination treatment rather than following the Bayesian toxicity monitoring plan. Unselected patients will continue to enroll on Arm A in a non-randomized fashion (up to 27 patients in total in Arm A) and patients with CDK12 loss subsequently enrolled on Arm C after the 5 patients treated with atezolizumab monotherapy will receive abemaciclib 200 mg BID as monotherapy (total enrollment on Arm C up to 21 patients in total).

TABLE OF CONTENTS

ABBREVIATIONS 2

SUMMARY OF CHANGES....4

SCHEMA 8

SYNOPSIS 8

TABLE OF CONTENTS....15

1. OBJECTIVES 19
   - 1.1 Study Design....19
   - 1.2 Primary Objectives....20
   - 1.3 Secondary Objectives....20
   - 1.4 Exploratory/Translational Objectives....20

2. BACKGROUND....20
   - 2.1 Study Disease(s)....20
   - 2.2 IND Agent(s)....22
   - 2.3 Rationale....22
   - 2.4 Correlative Studies Background....27

3. PARTICIPANT SELECTION....29
   - 3.1 Eligibility Criteria....29
   - 3.2 Additional Inclusion Criteria (Arm C patients)....31
   - 3.3 Exclusion Criteria....31
   - 3.4 Inclusion of Women and Minorities....35

4 REGISTRATION And Randomization PROCEDURES....35
   - 4.1 General Guidelines for DF/HCC Institutions....35

4.2 Registration Process for DF/HCC Institutions....36
4.3 General Guidelines for Other Investigative Sites....36
4.4 Registration Process for Other Investigative Sites....36

5. TREATMENT PLAN....37
5.1. Treatment Regimen....37
5.2. Pre-Treatment Criteria....38
5.3. General Concomitant Medication and Supportive Care Guidelines....39
5.4 Criteria for Taking a Participant Off Protocol Therapy....40
5.5 Duration of Follow Up....41
5.6 Criteria for Taking a Participant Off Study....41
5.7 Patient Replacement....42
5.8 Treatment Beyond Progression....42

6. DOSING DELAYS/DOSE MODIFICATIONS....42
6.1 Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab....44
6.2 Abemaciclib Toxicity Management....66

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS....72
7.1 Expected Toxicities....72
7.2 Adverse Event Characteristics and Definitions....72
7.3 Dose-Limiting Toxicities (DLT)....79
7.4 Adverse Event Reporting....81
7.5 Reporting procedures to Eli Lilly....82
7.6 Reporting Procedures to Genentech....83
MedWatch 3500A Reporting Guidelines....83
7.7 Reporting to Hospital Risk Management....85
7.8 Routine Adverse Event Reporting....85
7.9 Study Close-Out....85
7.10 Queries....86
7.11 Signal Management and Risk Management....86
7.12 Compliance with Pharmacovigilance Agreement / Audit....86

8. PHARMACEUTICAL INFORMATION....87
8.1 Abemaciclib....87
8.2 Atezolizumab....89

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES....91
9.1 Tissue Collection....91
9.2 Blood Collection....92
9.3 Specimen Banking....93
9.4 Analysis Plan for Correlative Studies....93

10. STUDY CALENDAR....94

11. MEASUREMENT OF EFFECT 97
11.1 Antitumor Effect 97
11.2 Radiographic Disease Criteria 104

12. DATA REPORTING / REGULATORY REQUIREMENTS 105
12.1 Data Reporting 105
12.2 Data Safety Monitoring 105
12.3 Multi-Center Guidelines 106

13. STATISTICAL CONSIDERATIONS 106
13.1 Study Design/Endpoints 106
13.2 Primary Efficacy Endpoint Statistical Plan and Sample Size 107
13.3 Primary Safety Endpoint Statistical Plan 108
13.4 Secondary Endpoint Analysis Plan 109
13.5 Statistical Plan for Primary Exploratory Endpoint Requiring Biopsies 110

14. PUBLICATION PLAN 110

REFERENCES 111

APPENDIX A PERFORMANCE STATUS CRITERIA 118

APPENDIX B MULTI-CENTER GUIDELINES 119

B-1. INTRODUCTION 119
B-1.1 Purpose 119

B-2. GENERAL ROLES AND RESPONSIBILITIES 119
B-2.1 Coordinating Center 119
B-2.2 External Site 120

B-3. DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS 121
B-3.1 Protocol Revisions and Closures 121
B-3.2 Informed Consent Requirements 121
B-3.3 IRB Re-Approval 122
B-3.4 DF/HCC Multi-Center Protocol Confidentiality 122
B-3.5 Participant Registration and Randomization 122
B-3.6 Initiation of Therapy 123
B-3.7 Eligibility Exceptions 123
B-3.8 Data Management 123
B-3.9 Protocol Reporting Requirements 123

B-4. MONITORING: QUALITY CONTROL 124
B-4.1 Ongoing Monitoring of Protocol Compliance 124
B-4.2 Monitoring Reports 125
B-4.3 Accrual Monitoring 125

B-5. AUDITING: QUALITY ASSURANCE 125
B-5.1 DF/HCC Internal Audits 125
B-5.2 Audit Notifications.....126
B-5.3 Audit Reports 126
B-5.4 External Site Performance 126

Appendix C 127

Appendix D 128

Appendix E 129

Appendix F 130

1. OBJECTIVES

1.1 Study Design

This is a multi-center, open label Phase II study of patients with metastatic castration resistant prostate cancer (mCRPC) treated with abemaciclib monotherapy, atezolizumab monotherapy or with combination therapy of abemaciclib and atezolizumab.

An unselected mCRPC cohort was initially randomized in a 1:1 fashion, to either abemaciclib monotherapy (Arm A) dosed at 200 mg orally BID each day during the 21-day cycle, or combination therapy (Arm B) of atezolizumab 1,200 mg IV once every 21 days and abemaciclib dosed at 150 mg orally BID each day during the 21-day cycle. Enrollment to Arm B was halted, so subsequent unselected patients are enrolled to Arm A in a non-randomized fashion. Enrollment to the unselected mCRPC cohort will be halted for efficacy analysis after 12 patients have been enrolled on Arm A of the study. After the efficacy interim analysis, if the efficacy threshold is achieved, then non-randomized, single-arm accrual will continue.

An exploratory cohort of mCRPC patients with CDK12 loss (Arm C) will be enrolled as follows: the first 5 patients will receive atezolizumab monotherapy 1,200 mg IV every 21 days. Subsequently an additional 16 patients were planned to receive a combination of atezolizumab 1,200 mg IV once every 21 days and abemaciclib dosed at 150 mg orally BID each day during the 21-day cycle; however enrollment to combination treatment was halted and the subsequent 16 patients will instead receive abemaciclib dosed at 200 mg orally BID each day during the 21-day cycle.

Bayesian toxicity monitoring was planned to be used for all patients enrolled to Arm B and to the combination treatment cohort of Arm C (up to a maximum of 43 patients) as detailed in Statistical Considerations. If the rate of patients experiencing dose limiting toxicities (DLTs) at the starting dose exceeded the pre-specified threshold for excessive toxicity, then subsequent patients randomized to Arm B or enrolled to the combination cohort of Arm C were planned to receive abemaciclib at one dose level reduction (100 mg BID) with atezolizumab 1200 mg every 21 days. If the rate of patients experiencing DLT at the reduced dose exceeded the pre-specified threshold for excessive toxicity, then enrollment to Arm B and the combination cohort of Arm C was planned to be halted. Due to two grade 5 sepsis events observed in the 8 patients treated on Arm B with unclear relationship to the study medications, the Sponsor-Investigator and co-investigators elected to halt enrollment to combination treatment rather than following the Bayesian toxicity monitoring plan. Unselected patients will continue to enroll on Arm A in a non-randomized fashion (up to 27 patients in total in Arm A) and patients with CDK12 loss subsequently enrolled on Arm C after the 5 patients treated with atezolizumab monotherapy will receive abemaciclib 200 mg BID as monotherapy (total enrollment on Arm C up to 21 patients in total).

All patients will undergo an on-treatment biopsy after six weeks of therapy. Treatment will be continued until disease progression and/or Section 5.4 criterion is met.

1.2 Primary Objectives

- To determine the efficacy of abemaciclib monotherapy in biomarker-unselected patients with metastatic CRPC (Arm A).
- To determine the efficacy of abemaciclib in combination with atezolizumab in biomarker-unselected patients with metastatic CRPC (Arm B).
- To determine the safety of abemaciclib in combination with atezolizumab in mCRPC (Arm B).

1.3 Secondary Objectives

- To evaluate secondary measures of clinical efficacy of abemaciclib monotherapy and abemaciclib (Arm A) in combination with atezolizumab (Arm B) in biomarker-unselected cohort.
- To identify the clinical variables associated with response and resistance to therapy including type of prior antiandrogen therapy (CYP17 inhibitor or AR antagonist), duration since prior antiandrogen therapy, receipt of prior chemotherapy, and visceral- versus bone- predominant disease (Arms A and B).
- To determine the safety and adverse event profiles of abemaciclib monotherapy and abemaciclib in combination with atezolizumab in mCRPC (all Arms).

1.4 Exploratory/Translational Objectives

- To assess the efficacy of atezolizumab alone and abemaciclib monotherapy in the CDK12 loss cohort (Arm C).
- Primary translational objective: To assess FoxP3+/CD8+ ratio in all biopsy specimens and the change between pre-treatment and on-treatment specimens will be reported descriptively for each treatment arm separately (all Arms).
- To perform detailed profiling of tumor immune infiltrate from paired baseline (where available) and on-treatment tumor biopsies in biomarker-unselected and CDK12 mutant cohorts (all Arms).
- Evaluate changes in androgen-receptor signaling pathway with exposure to abemaciclib monotherapy and abemaciclib in combination with atezolizumab (all Arms).
- Identify the biomarkers of response and resistance to abemaciclib monotherapy and in combination with atezolizumab in biomarker-unselected patients (Arms A and B).

2. BACKGROUND

2.1 Study Disease(s)

Prostate cancer is the most common non-cutaneous malignancy and second most common cause of cancer death in men in the United States (1). The backbone of systemic treatment for metastatic prostate cancer is androgen deprivation therapy (ADT), most commonly accomplished through agonists or antagonists of luteinizing hormone releasing hormone (LHRH). However,

depth and duration of response to ADT is highly variable, and eventual resistance to ADT, i.e. progression to metastatic castration-resistant prostate cancer (mCRPC) is nearly universal. Castration-resistant prostate cancers most commonly remain dependent on signaling through the androgen receptor (AR), and secondary AR pathway-targeted therapies abiraterone (2, 3) and enzalutamide (4, 5) have demonstrated overall survival benefit in mCRPC. Other agents that have demonstrated overall survival benefit in Phase III studies in mCRPC include the chemotherapeutics docetaxel (6) and cabazitaxel (7), the immunotherapeutic Sipuleucel-T (8), the radiopharmaceuticals Radium-223 (9) and ^{177}Lu-PSMA-617 (10), and the PARP inhibitor olaparib (in patients with pathogenic *BRCA1/2* and *ATM* alterations) (11). However, patients eventually progress through these therapies and succumb to their disease, and thus novel therapeutic approaches to treating mCRPC is a major clinical need.

The genetic landscapes of both primary prostate cancer (12) and mCRPC (13) have been characterized, and have nominated oncogenic drivers of prostate cancer, as well as mechanisms of resistance to ADT and potential therapeutic targets in mCRPC. For example, genetic alterations in the *AR* gene locus (including amplifications, point mutations, or structural variants (14)) and the presence of ligand-independent splice variants (such as AR-v7 (15)) seen in mCRPC have been implicated in resistance to ADT. In addition, other genetic alterations involving the AR, PTEN/PI3K (Phosphatase and Tensin Homolog/Phosphatidylinositol 3-kinase), Wnt/β-catenin, and cell cycle pathways, as well as genes involved in DNA damage repair and epigenetic modulation are commonly seen in metastatic castration-resistant prostate cancer (13) and are enriched in mCRPC compared to primary treatment-naïve prostate cancer (16, 17).

Despite this extensive genetic characterization, clinical benefit to molecularly targeted agents other than those targeting the androgen receptor has so far been limited primarily to genetically-defined subsets of patients with mCRPC with defects in DNA repair pathways. The immune checkpoint inhibitor immunotherapy (CPI) pembrolizumab is approved for use in unresectable or metastatic microsatellite instability–high (MSI-H) or mismatch repair deficient (dMMR) solid tumors progressing following prior treatment and who have no satisfactory alternative treatment options (18), and can thus be prescribed for the subset of patients with mCRPC with this phenotype. In addition, patients with deleterious alterations in genes involved in homologous recombination repair (HRR) can respond to inhibitors of Poly (ADP-ribose) polymerase (PARP) (19, 20) – the FDA has approved olaparib for patients with HRR gene mutations and rucaparib for patients with deleterious mutations involving *BRCA1* or *BRCA2*. However, only ~3% of patients with mCRPC are phenotypically MSI-H/dMMR (21), and only ~18-20% have mutations in *BRCA1*, *BRCA2* or *ATM* (16, 17) – even in these subpopulations responses to pembrolizumab (21, 22) and PARP inhibitors (19, 20) are not universal. As such, alternative paradigms for molecularly targeted therapy in mCRPC warrant exploration.

Genetic alterations involving cell cycle signaling are common in mCRPC (13) and may contribute to resistance to AR-targeted therapies (23). Inhibitors of cyclin-dependent kinases 4 and 6 have demonstrated anti-tumor activity in multiple pre-clinical models of castration-resistant prostate cancer (24, 25), and have demonstrated synergistic activity with CPIs directed against PD-1 (Programmed Death 1) or PD-L1 (Programmed Death Ligand 1) in pre-clinical models of many cancer types (26-29). Herein, we propose a phase II study of the CDK4/6 inhibitor abemaciclib with or without the anti-PD-L1 antibody atezolizumab in mCRPC resistant

to secondary AR-targeted therapy.

2.2 IND Agent(s)

2.2.1 Abemaciclib

Abemaciclib is an oral inhibitor of cyclin-dependent kinases (CDK4 and CDK6). Binding to Cyclin D activates CDK4 and CDK6, which in turn promote retinoblastoma protein (Rb) phosphorylation, leading to cell cycle progression and cell proliferation via an E2F mediated mechanism. Through inhibition of CDK4 and CDK6, abemaciclib prevents Rb phosphorylation and subsequently results in cellular apoptosis.

Abemaciclib is FDA-approved for the treatment of women with hormone-receptor positive, HER2-negative breast cancer, in combination with endocrine therapy for adjuvant treatment of node-positive early breast cancer at high risk of recurrence and a Ki-67 score ≥20%, in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women or in combination with fulvestrant after disease progression on endocrine therapy for metastatic breast cancer, and as monotherapy in the same patient population after progression on endocrine therapy but prior to systemic chemotherapy administration.

The most common adverse events associated with abemaciclib observed in ≥ 20% of the study population are diarrhea, neutropenia, nausea, abdominal pain, infections, fatigue, anemia, leukopenia, decreased appetite, vomiting, headache, and thrombocytopenia.

2.2.2 Atezolizumab

Atezolizumab is a PD-L1 monoclonal antibody. Inhibiting the immune suppressive interaction of PD-L1 on tumor cells or tumor infiltrating immune cells and PD-1 on T cells has been shown in multiple cancer types to result in an increased anti-tumor immune response.

Atezolizumab has been FDA-approved in metastatic non-small cell lung cancer with disease progression during or after receiving platinum-containing chemotherapy, and more recently for first-line treatment of non-small cell lung cancer, small-cell lung cancer.

The most common adverse effects associated with atezolizumab observed in ≥ 20% of the urothelial carcinoma study population were fatigue, decreased appetite, nausea, constipation, urinary tract infection, diarrhea, and pyrexia, and in the metastatic non-small cell lung cancer population were fatigue, decreased appetite, dyspnea and cough.

2.3 Rationale

2.3.1 Rationale for CDK4/6 inhibition in mCRPC

Cell cycle signaling mediated through cyclin dependent kinases 4 and 6 (CDK4/6) is a critical pathway conferring oncogenic phenotypes in multiple cancer types. Small molecule inhibitors of

CDK4/6, including abemaciclib, palbociclib and ribociclib have already been FDA approved for the treatment of metastatic hormone receptor-positive HER2-negative breast cancer (30). In pre-clinical models of castration-resistant prostate cancer (CRPC), inhibitors of CDK4/6 have demonstrated single-agent activity in enzalutamide-resistant cells *in vitro* (24) and in CRPC *in vivo* model systems (25). Activity was seen even in the context of alterations in AR commonly seen as resistance mechanisms in mCRPC, including AR-V7 splice variant expression, the AR F876L mutation, and loss of AR expression. A genome-wide open reading frame (ORF) screen identified CDK4 and CDK6 as mediators of resistance to enzalutamide in LNCaP cells, and whole exome sequencing of paired pre-treatment and post-treatment biopsies obtained from patients treated with enzalutamide suggest the CDK4/6 pathway as a mediator of both intrinsic and acquired resistance to androgen-receptor targeted therapy (23).

Multiple clinical trials of CDK4/6 inhibitors in prostate cancer are ongoing including 1) palbociclib monotherapy in mCRPC (NCT02905318), 2) palbociclib with ADT for metastatic RB1 (retinoblastoma)-proficient castration-sensitive prostate cancer (NCT02059213), 3) ribociclib with docetaxel in mCRPC (NCT02494921), 4) enzalutamide with or without ribociclib in mCRPC (NCT02555189), 5) abiraterone with or without abemaciclib in 1st line mCRPC (NCT03706365) and 6) abemaciclib in men with heavily treated mCRPC (NCT04408924).

Abemaciclib has some mechanistic differences compared with palbociclib and ribociclib including a higher potency in inhibiting CDK4 and CDK6 and greater specificity for CDK4 *in vitro*, and demonstrates some inhibitory activity against CDK9 as well (31, 32). Clinically, abemaciclib has lower rates of bone marrow suppression, which allows for an uninterrupted delivery of therapy, compared with palbociclib and ribociclib, which require a 1 week break after 3 weeks of therapy for recovery of the bone marrow function (33). In metastatic hormone receptor-positive, HER2-negative breast cancer, palbociclib (34), ribociclib (35) and abemaciclib (36) are all FDA-approved in combination with aromatase inhibition for 1st line treatment; however, only abemaciclib is approved as monotherapy in treatment-resistant patients (37).

Given this experience in breast cancer, along with evidence that CDK4/6 signaling is associated with resistance to secondary AR-targeted therapy in mCRPC (23) and that CDK4/6 inhibitors demonstrate single agent activity in pre-clinical models (24, 25), abemaciclib warrants study both as a single agent and in combination with other agents in therapy-resistant mCRPC.

2.3.2 Rationale for anti-PD1/PD-L1 checkpoint immunotherapy in mCRPC

While anti-PD1/PD-L1 checkpoint inhibitor immunotherapies (CPIs) have demonstrated remarkable anti-tumor activity in multiple cancer types, the activity of these agents as monotherapy in prostate cancer is modest. In an early report of 296 patients with metastatic solid tumors treated with the anti-PD-1 antibody BMS-936558 (nivolumab), no objective responses were seen in patients with castration-resistant prostate cancer (38). However, in the KEYNOTE-028 study of the anti-PD-1 antibody pembrolizumab in treatment-resistant mCRPC patients with measurable disease and PD-1 ligand (PD-L1) expression in ≥1% of tumor or stromal cells (39), 4 of 23 patients experienced radiographic response (overall response rate = 17.4%) while 8 of 23 patients (34.8%) had stable disease.

The KEYNOTE-199 study of pembrolizumab monotherapy in metastatic CRPC (Cohort 1 - PD-L1 positive measurable disease; cohort 2 - PD-L1 negative measurable disease; and Cohort 3 -

bone-only disease) (40) also reported modest clinical activity in this population. The response rate per central radiology review across Cohorts 1 and 2 was 5% (although 10% of patients with measurable disease achieved a >30% reduction in sum of target lesions from baseline), and the rate of PSA reduction by >50% across cohorts 1-3 was about 10%. No obvious biomarkers were identified that correlated with response to pembrolizumab, though alterations in genes involved in DNA damage response were identified in some of the responders. Of the 6 patients with available genetic sequencing data among the 9 responders in KEYNOTE-199, only 1 showed evidence for an alteration in a gene involved in mismatch repair (*MLH3* T930Qfs*35 deletion in patient 1). As such, pembrolizumab can have clinical activity even in patients without an MSI-high/dMMR phenotype.

Some hypotheses for why prostate cancer is less responsive to anti-PD-1/PD-L1 CPI than other tumor types include relatively low tumor mutational burden (41), low/variable expression of PD-L1 (42), and low T cell cytolytic activity in prostate tumors (43). Thus, strategies to promote a cytolytic immune infiltrate in prostate cancer (i.e. rendering immunologically "cold" tumors "hot") to increase likelihood of response to CPI are of great interest. One strategy to increase immunogenicity of prostate cancer tumors is combining anti-PD-1/PD-L1 CPI with enzalutamide based on pre-clinical findings that resistance to enzalutamide was associated with increased levels of tumor-intrinsic PD-L1, and that patients progressing on enzalutamide had significantly increased PD-L1/2+ dendritic cells (DC) in blood compared to those naïve or responding to treatment (44). In an early study of pembrolizumab administered in combination with enzalutamide (45), 5 of the first 28 patients experienced a response; of the 3 patients with available genetic sequencing data among the 5 responders, only one was found to be MSI-high. The combination of pembrolizumab and enzalutamide has been further explored in Cohorts 4 and 5 of KEYNOTE-199 (NCT02787005) (46) and cohort C of KEYNOTE-365 (NCT02861573) (47), with preliminary evidence for activity such that Phase 3 trials of pembrolizumab vs. placebo in combination with enzalutamide are currently in progress for patients with patients with metastatic hormone-sensitive prostate cancer (NCT04191096) and mCRPC (NCT03834493).

The IMbassador250 study of enzalutamide with or without atezolizumab in abiraterone-resistant mCRPC (NCT03016312) (48) did not demonstrate an overall survival benefit to atezolizumab compared to placebo in this unselected patient population. A variety of other strategies to increase the activity of atezolizumab in mCRPC are currently being explored including combination with the autologous dendritic cell vaccine Sipuleucel-T (NCT03024216), the alpha particle-emitting radiopharmaceutical Radium-223 (NCT02814669) (49), the AKT inhibitor ipatasertib (NCT03673787), and the multi-kinase inhibitor cabozantinib (NCT03170960). In particular, the combination of atezolizumab with cabozantinib in the COSMIC-021 study (50) has demonstrated promising clinical activity with an overall response rate per RECIST 1.1 among the 44 pts of 32% (2 CRs [4.5%] and 12 PRs [27%]); 21 (48%) pts had SD resulting in a disease control rate of 80% in all patients.

However, the relative merits of these various approaches are not currently known, and biomarkers identifying patients likely to benefit from particular strategies have yet to be identified. Thus, other combination strategies warrant investigation, along with companion translational studies to explore the biology of novel combinations and establish predictive biomarkers.

2.3.3 Rationale for CDK4/6 inhibitor in combination with anti-PD-L1 checkpoint inhibition

The combination of abemaciclib with atezolizumab is a potentially promising therapeutic strategy in mCRPC, as multiple preclinical studies have demonstrated synergy between CDK4/6 inhibition and anti-PD-1/PD-L1 targeted immunotherapy. In a breast cancer model, abemaciclib led to enhanced tumor antigen presentation and suppressed the proliferation of regulatory T cells, triggering anti-tumor immunity – abemaciclib showed synergistic activity with anti-PD-L1 targeted therapy in this model (26). A second report suggested that CDK4/6 inhibition increased PD-L1 protein levels by impeding its degradation; synergistic activity of CDK4/6 inhibition with anti-PD-1 immunotherapy was seen in this study as well (27). In a third report, single-cell RNA sequencing (scRNA-seq) from 33 melanoma tumors identified a resistance program expressed by malignant cells that is associated with T cell exclusion and immune evasion. Abemaciclib was shown to repress this immune resistance program, and the combination of abemaciclib with anti-PD-1 and anti-CTLA4 monoclonal antibodies demonstrated synergistic activity in a xenograft model (28). A fourth report demonstrated in an immunocompetent syngeneic mouse model that abemaciclib increased a T cell inflammatory signature in tumors. The combination of abemaciclib with anti-PD-L1 therapy led to complete tumor regressions and immunological memory, accompanied by enhanced antigen presentation, a T cell inflamed phenotype, and enhanced cell cycle control (29).

Clinically, preliminary safety and efficacy of the combination of abemaciclib with the anti-PD-1 CPI pembrolizumab (I3Y-MC-JPCE; NCT02779751) has been reported for KRAS mutated PD-L1 positive non-small cell lung cancer (NSCLC) (Arm A) and squamous NSCLC (Arm B)(51), as well as for hormone receptor positive, HER2 negative (HR+ HER2-) metastatic breast cancer as a two-drug combination (Arm C) (52) and as a three-drug combination with anastrozole (Arm D) (53). Clinical activity was seen in all four cohorts, with the activity of abemaciclib plus pembrolizumab in HR+ HER2- breast cancer (Arm C) appearing particularly promising with 29% overall response rate, 82% disease control rate (complete response [CR]+partial response [PR]+stable disease [SD]), and 46% clinical benefit rate (CR+PR+SD persisting for ≥6 months).

Adverse effects of the combination in I3Y-MC-JPCE were similar to what would be expected for the single agents, except for a higher than expected rate of grade 3 or higher elevations in liver function tests (LFTs), which were reversible upon discontinuation, and interstitial lung disease (ILD)/pneumonitis events. Grade 3 or higher increase of alanine aminotransferase (ALT) was seen in 24% of patients in Arm A, 0% in Arm B, 11% in Arm C, and 31% in Arm D; grade 3 or higher ILD/pneumonitis was seen in 3 patients in Arm A, 1 patient in Arm B, not reported for Arm C, and 2 patients in Arm D who subsequently died as a result of pneumonitis.

There are key differences in patient population and choice of CPI between I3Y-MC-JPCE and the current trial. A recent meta-analysis reported the incidence of grade >= 3 adverse events to be greater for anti-PD-1 agents compared to anti-PD-L1 agents (OR 1.58; 95% CI 1.00-2.54) (54). In similar patient populations (understanding the limitations of cross-trial comparisons), incidence of grade >=3 pneumonitis appeared to be numerically higher with anti-PD-1 agents in trials of monotherapy in urothelial carcinoma (2.3% for pembrolizumab in KEYNOTE-045 (55), none reported for atezolizumab in IMvigor211 (56)) and in PD-L1+ NSCLC (2.6% for pembrolizumab in KEYNOTE-010 (57), 1% for avelumab in JAVELIN Lung 200 (58)), and in

combination trials with chemotherapy in non-squamous NSCLC (3% for pembrolizumab in KEYNOTE-189 (59), 2% for atezolizumab in IMpower132 (60)) and in squamous NSCLC (2.5% for pembrolizumab in KEYNOTE-407 (61), 1% for atezolizumab in IMpower131 (62)). Safety data of the combination of abemaciclib with an anti-PD-L1 CPI (such as atezolizumab, avelumab or durvalumab) has yet to be reported.

The risk of anti-PD-1 related pneumonitis has been reported to be higher in patients with lung cancer than patients with other metastatic malignancies (63, 64). In addition, a recent analysis of pooled data from 66 prospective trials of CPIs submitted to the FDA suggested an increased risk of pneumonitis in patients who received radiation therapy (65). As such, excluding patients with history of lung cancer or radiation to the thorax, as well as current smokers/patients with extensive smoking history (> 20 pack years), prior ILD/pneumonitis and those with evidence for baseline restrictive pattern on pulmonary function testing is likely to prevent those patients most likely to experience treatment-related pneumonitis from enrolling on the study.

Promising clinical activity of cabozantinib with atezolizumab in mCRPC seen in the COSMIC-021 study (50) is a proof-of-concept that atezolizumab combinations may be effective in this disease setting. As the proposed mechanism of immune modulation is distinct for CDK4/6 inhibitors vs. cabozantinib, these inhibitors may benefit different patient populations. Findings from the pre-clinical studies summarized above as well as from Arm C of I3Y-MC-JPCE in HR+ HER2- breast cancer (given biological similarities with prostate cancer as a hormonally-driven epithelial cancer with limited efficacy of pembrolizumab as monotherapy) would suggest that the combination of CDK4/6 inhibition with anti-PD-1/PD-L1 checkpoint immunotherapy warrants study in mCRPC.

2.3.4 Rationale for investigation in CDK12 mutant mCRPC

Whole exome and transcriptome sequencing have extensively characterized the mCRPC genomic landscape (13, 66). A novel subset of prostate cancer typified by biallelic inactivation of CDK12 has been identified at a frequency of 6.7% in mCRPC (67, 68) and is associated with aggressive clinical behavior (69). CDK12 biallelic loss is characterized by focal tandem duplications and a large number of gene fusions, which has been shown to be associated with gains in cell cycle and DNA replication genes, including CCND1. In addition, mCRPC with biallelic loss has a higher neoantigen burden than other subtypes of advanced prostate cancer, suggesting a potentially increased sensitivity to checkpoint inhibitor therapy (68, 70, 71). CDK12 and CDK13 are associated with cyclin K and play a role in regulating transcription elongation and RNA splicing. In an evaluation of CDK12 gene modification prevalence across various tumor types, there was a 1.08% mutation rate across 1203 prostate cancer samples, compared with 2.3% in 915 ovarian cancer samples (72). Impairing CDK12 function in ovarian cancer cells has been shown to decrease BRCA1 levels and disrupt homologous recombination repair, leading to reported increased sensitivity to cisplatin and PARP inhibition (73). In a series of 556 ovarian carcinomas, 17 tumors were found to have markedly increased genomic copy number, with 15 of these 17 cases also harbored CDK12 mutations, the majority of which were deleterious (74).

D-type cyclins, in particular cyclin D1 (CCND1), function to regulate CDK4/6 activity (30). While amplification of CCND1 has been inconsistently predictive of response to CDK4/6

inhibition in the literature, CCND1 upregulation in mCRPC with biallelic CDK12 loss nonetheless suggests response to CDK4/6 inhibitors, as CCND1 amplification is indicative of increased CDK4/6 activity.

2.3.5 Hypotheses:

1. Abemaciclib monotherapy will demonstrate clinical efficacy in patients with biomarker-unselected metastatic CRPC.
2. Exploratory: Atezolizumab alone will demonstrate clinical efficacy in patients with CDK12-mutant metastatic CRPC.

2.4 Correlative Studies Background

2.4.1 ImmunoProfile

Based on pre-clinical studies suggesting that abemaciclib can alter the immune microenvironment in tumors (26, 29), we plan to characterize immune infiltrate in biopsy specimens obtained 6 weeks after starting on trial therapy using the ImmunoProfile assay at Dana-Farber Cancer Institute (DFCI). This assay is already being used to develop an in-depth database of immunoprofiles for all patients seen at DFCI, Brigham and Women's Hospital, and Boston Children's Hospital to better predict response to immunotherapies. This is an optimized multiplex immunofluorescence assay performed in a Clinical Laboratory Improvement Amendments (CLIA) environment with standardized reporting across all samples for research or standard clinical care. The report includes levels of a particular biomarker in both tumor and tumor-stroma interface compartments; PD-L1 expression is reported for both malignant cells and inflammatory cells. As a research test in the same environment, we plan to assay for FoxP3, CD8, PD-L1, and Granzyme B expression, with DAPI as a counterstain. FoxP3 is a marker of regulatory T cells, whereas CD8 is a marker of cytotoxic T-cells; Goel et al. (26) reported a significant decrease in FoxP3+/CD8+ ratio in a tumor model with abemaciclib treatment compared to vehicle control, which was proposed to be one mechanism by which CDK4/6 inhibition may synergize with anti-PD1/PD-L1 checkpoint inhibitor immunotherapy.

The primary biomarker endpoint of this study is the change in FoxP3+/CD8+ ratio in on-treatment biopsy specimens compared to matched archival metastatic biopsy specimens from the same patient (when available) in patients treated with abemaciclib and atezolizumab (arm B) or with abemaciclib alone (arm A). We will also explore correlation of immune infiltrate with genetic features as described below.

2.4.2 Targeted exome sequencing from tumor biopsy

Whole exome sequencing in mCRPC has characterized the genetic landscape of this disease state and has identified potential biomarkers for prediction of therapeutic vulnerabilities (13, 16, 75). University of Minnesota team is validating a CRPC-biology panel that consists of androgen-receptor gene and its targets, and genes that are known or are considered highly likely to be important in disease progression, treatment response or resistance (AR, PTEN, TP53, RB, E2F, ATM, ATR, BARD1, BLM, BRCA1, BRCA2, BRIP1, CHEK2, MRE11A, MSH2, MSH6, NBN, PALB2, PMS2, RAD51, RAD51B, RAD51C, RAD51D, RAD54L, RBBP8, SLX4, and

XRCC2). We will correlate genetic features from biopsy specimens with response and resistance to therapy. Specifically, we would predict that a combination of aberrant AR signaling and alterations in the CDK4/6 pathway (i.e. amplifications of CCND1, CCND3, CDK4, CDK6; deletions of CDKN2A) would correlate with response to abemaciclib in this study (33). Loss of RB1 or amplification of CCNE1 would be predicted to correlate with resistance to abemaciclib monotherapy (76), but may not necessarily lead to resistance to abemaciclib + anti-PD-L1 given that the mechanism of immune activation by CDK4/6 inhibition may be independent of these alterations.

In addition, we would predict that alterations in genes involved in DNA damage repair, particularly those that would lead to an increase in neoantigen burden, would correlate with response to checkpoint inhibitor immunotherapy (77). These are included in the CRPC-biology panel and we will correlate loss-of-function alterations in these genes with response and resistance to therapy, as well as with composition and changes in immune infiltrate.

2.4.3 Whole transcription sequencing from tumor biopsy

Whole transcriptome sequencing from tumor specimens can be used both to identify variant transcripts not easily assessed by DNA sequencing alone (such as splice variants or transcriptional products of genetic structural alterations/rearrangements). This will help identify the locations of canonical and aberrant AR splicing events (14) and allow determination of expression profiles a broad array of genes involved in AR signaling and cell cycle regulation. We would hypothesize that cancers that express a T cell-inflamed gene expression signature upon treatment with abemaciclib with or without atezolizumab would be more likely to respond to checkpoint immunotherapy.

2.4.4 Whole transcriptome sequencing from exosomes

Serial assessment of tumor biology in prostate cancer is challenging due to bone-predominant metastatic disease in a majority of patients. This results in a lower biopsy yield, loss of RNA and phosphorylated proteins due to specimen processing. “Liquid biopsy” approaches have gained traction in the field as these allow sequential characterization with low burden to the patient. More commonly used approaches have certain limitations including low CTC yield in patients with lower burden of disease and lack of RNA and proteins for analysis with cfDNA approaches. Tumor-derived circulating blood exosomes have thus emerged as an area of interest. Whole transcriptome sequencing from exosomes derived from blood is feasible and can detect tumor-specific transcripts (78). Advantages of a blood-based biomarker include the ability to sample from a patient’s entire tumor burden rather than a single metastatic site, and greater ease in monitoring changes over time (i.e. pre-treatment, on-treatment and at progression).

2.4.5 Tumor Profiling from circulating free DNA (cfDNA)

Analysis of circulation cell-free DNA (cfDNA) is a promising approach to genetic characterization of a patient’s tumor burden over time. Sparse whole genome sequencing at 0.1x coverage, termed ultra-low pass whole genome sequencing (ULP-WGS), can be used to identify copy number alterations (CNA) in the tumor, as well as the tumor fraction (i.e. percentage of

cfDNA derived from tumor rather than non-cancerous tissues), using an algorithm called ichorCNA (79).

In addition, comprehensive genomic characterization can be performed through whole exome sequencing (79) and targeted sequencing panels (80). We have designed a custom bait set specifically for prostate cancer including allowing for identification of SSNVs in all genes known to be recurrently mutated in metastatic prostate cancer (16), genes involved in DNA damage repair, as well as sequencing of intronic and intergenic regions of genes known to be translocated or have complex structural alterations in prostate cancer (AR (14), ERG, TMPRSS2, ETV1, ETV4, SLC45A3, RAF1). We plan to perform targeted next generation sequencing from circulating free DNA at baseline, at 6 weeks, and at progression. This analysis will allow us to identify alterations at baseline not detected from the tumor biopsy (i.e. if DNA from tumor biopsy is insufficient or if alterations are derived from other non-sampled metastatic sites), and will allow us to detect new alterations at the time of progression to nominate mediators of resistance.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

3.1.1 Diagnosis of metastatic castration resistant prostate cancer (mCRPC), with histologic confirmation of adenocarcinoma of the prostate (without evidence of small cell carcinoma), with progressive disease at the time of study entry by either

- Sequence of at least 2 rising PSA values at a minimum of 1-week intervals
- Radiographic progression per RECIST1.1 for soft tissue and/or per PCWG3 (81) for bone, with or without PSA progression

3.1.2 Adult males 18 years of age or older.

3.1.3 ECOG performance status of 0 or 1

3.1.4 Patients must have metastatic disease by bone scintigraphy or other nodal or visceral lesions on CT or MRI with a bone or soft tissue lesion amenable to image-guided percutaneous biopsy at acceptable risk for research biopsy per institutional standards, and the patient must be evaluable for disease response by either

- Baseline PSA $\geq$ 2.0 ng/mL OR
- Measurable disease per RECIST 1.1

3.1.5 Past progression or intolerance to at least one novel antiandrogen therapy (abiraterone, enzalutamide, galeterone, apalutamide, darolutamide, orteronel, seviteronel or equivalent) in either the hormone-sensitive or castration-resistant disease setting.

3.1.6 Not a candidate for docetaxel or cabazitaxel chemotherapy due to:
- progression within 12 months of completion or intolerance to prior taxane OR
- refusal of taxane OR
- contraindication to, or lack of fitness for taxane OR
- Investigator assessment that taxane is not clinically indicated or preferred.

3.1.7 Maintenance of castration status, defined as serum testosterone level of less than 50 ng/dL. Patients must be surgically castrate or maintained on LHRH agonist or antagonist therapy for the duration of the study period.

3.1.8 Must have recovered from any treatment-related toxicities to ≤ CTCAE grade 1.
- Patients with ≤ CTCAE grade 2 anorexia, alopecia, neuropathy, and/or fatigue however, are also permitted to enroll.

3.1.9 Participants must have adequate organ and marrow function as defined below:

- leukocytes ≥3,000/mcL
- absolute neutrophil count ≥1,500/mcL
- lymphocyte count ≥500/mcL
- hemoglobin ≥9 g/dL (without transfusion or growth factor in prior 28 days, except for patients assigned to atezolizumab monotherapy in Arm C for whom transfusion to meet this eligibility criterion is permitted)
- platelets ≥100,000/mcL (without transfusion or growth factor in prior 28 days)
- Serum albumin ≥ 25 g/L (2.5 g/dL)
- total bilirubin ≤1.5 × institutional upper limit of normal, unless the subject has known or suspected Gilbert's syndrome in which case total bilirubin must be ≤ 2 × ULN
- AST(SGOT)/ALT(SGPT) ≤1.5 × institutional upper limit of normal, except for patients assigned to atezolizumab monotherapy in Arm C for whom ≤2.5 × upper limit of normal is permitted
- INR and aPTT ≤1.5 × institutional upper limit of normal, unless the subject is receiving therapeutic anticoagulation, in which case they must be on a stable anticoagulant regimen
- creatinine clearance ≥30 mL/min/1.73 m2 (by Cockcroft-Gault formula or 24-hour urine collection)

3.1.10 Life expectancy of at least 6 months, as determined by a study Investigator.

3.1.11 Ability to swallow oral medications.

3.1.12 Ability to understand and willingness to sign an IRB-approved informed consent.

3.2 Additional Inclusion Criteria (Arm C patients)

3.2.1 Must have documentation (via CLIA approved, CAP certified next generation sequencing [NGS] assay report) of genomic aberration resulting in CDK12 loss of function in metastatic tumor tissue.

- Patients whose tumors have not previously undergone NGS are not eligible for Arm C but are eligible for the randomized unselected cohorts.

3.3 Exclusion Criteria

3.3.1 History of leptomeningeal disease, or clinical evidence of, or known and untreated metastatic CNS disease.

3.3.2 Concurrent active malignancy with the exception of malignancies with a negligible risk of metastasis or death (e.g., 5-year OS rate > 90%).

- Patients with adequately treated non-melanomatous skin cancer, cancer not needing active therapy for at least 2 years, cancer for which the treating investigator deems the subject to be in remission, or any prior malignancy that was treated with curative intent (no evidence of disease for at least 3 years) are also permitted to enroll.

3.3.3 Treatment with chemotherapy or radiotherapy within 4 weeks prior to planned cycle 1 day 1 of study treatment.

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

3.3.5 Treatment with oral anti-neoplastic intervention such as an oral hormonal agent, PARP inhibitor, or AR targeted therapy within 14 days prior to planned cycle 1 day 1 of study treatment.

3.3.6 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.

3.3.7 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.

3.3.8 Prior treatment with an inhibitor of CDK4 and/or 6.

3.3.9 Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti– CTLA-4, anti–PD-1, PD-L1, or PD-L2-therapeutic antibodies

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

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

3.3.12 Known allergy or hypersensitivity to any component of the abemaciclib formulation.

3.3.13 Patients on concurrent therapy with a moderate or strong CYP3A4 inducer or inhibitor which cannot be safely stopped at least five half-lives prior to initiation of therapy with abemaciclib.

3.3.14 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 (see Appendix E for a more comprehensive list of autoimmune diseases and immune deficiencies), with the following exceptions:

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

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

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

-Rash must cover < 10% of body surface area

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

-There has been 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

3.3.15 Prior allogeneic stem cell or solid organ transplantation

3.3.16 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

3.3.17 Active smoking (of tobacco, marijuana, or any other substance) or vaping at time of enrollment, or a history of smoking equivalent to greater than 20 pack-years of cigarettes (i.e. # packs of cigarettes [or equivalent per the below] smoked per day × # of years patient has smoked > 20).

Equivalents (per https://www.smokingpackyears.com/):

	1 pack/day equivalent (20 cigarettes/pack)	20 pack-year equivalent
Marijuana joints	10 / day	200 joint-years
Cigars	5 / day	100 cigar-years
Pipes	8 / day	160 pipe-years
Water pipe (20 minute session)	5 / day	100 water pipe-years

3.3.18 Prior history of radiation therapy to thorax (including to lungs/pleura, esophagus, intrathoracic lymph nodes, C7-L2 vertebrae, or ribs) for any reason and any duration/dose. This exclusion criterion does not apply to patients assigned to atezolizumab monotherapy in Arm C, who may have received prior radiation to thorax.

3.3.19 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

3.3.20 Active tuberculosis

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

3.3.22 Any history of lung cancer, regardless of stage or treatment

3.3.23 Any of the following abnormalities on pre-treatment pulmonary function testing:
a. FEV1/FVC ratio < lower limit of normal (LLN) and FEV1 < 75% predicted OR
b. FVC < 70% of predicted, regardless of FEV1/FVC ratio OR
c. DLCO (corrected for hemoglobin) < 70% of predicted

The LLN of the FEV1/FVC ratio, which recognizes the change with age of this measurement, is determined by subtracting 10% or 0.10 from the age-specific FEV1/FVC

predicted for any individual (82).

3.3.24 Uncontrolled tumor-related pain
-Patients requiring pain medication must be on a stable regimen at study entry.
-Symptomatic lesions (e.g., bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated prior to enrollment. Patients should be recovered from the 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.

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

3.3.26 Severe infection, or active known detectable viral infection (e.g., Human Immunodeficiency Virus [HIV] or viral hepatitis) within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia, or any active infection that could impact patient safety

3.3.27 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:
-Patients who received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study.
-Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease (COPD) or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study.

3.3.28 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.

3.3.29 Current treatment with anti-viral therapy for HBV.

3.3.30 Arterial or venous thromboembolic event within the last 3 months.

3.3.31 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 3 months prior to initiation of study treatment.

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

3.3.33 Significant infection, medical condition, or social situation which, in the opinion of the investigator, would preclude participation or limit the patient's ability to comply with study requirements.

3.4 Inclusion of Women and Minorities

Every effort will be made to include men from minority populations. The enrollment of minority men will reflect the proportion of minority subjects at the sites participating in the trial. Women are not affected by prostate cancer and therefore are not eligible.

4 REGISTRATION AND RANDOMIZATION PROCEDURES

4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of any protocol-specific therapy or intervention. Any participant not registered to the protocol before protocol-specific therapy or intervention begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

The eligibility checklist(s) and all pages of the consent form(s) will be faxed to the ODQ at 617-632-2295. The ODQ will (a) review the eligibility checklist, (b) register the participant on the protocol, and (c) randomize the participant.

Randomization can only occur during ODQ business hours (8:30am - 5pm Eastern Time, Monday through Friday excluding holidays).

An email confirmation of the registration and/or randomization will be sent to the study coordinator(s) from the registering site, treating investigator and registering person immediately following the registration and/or randomization.

Following registration, participants may begin protocol-specific therapy and/or intervention.

Issues that would cause treatment delays should be discussed with the Principal Investigator (PI) of the registering site. If the subject does not receive protocol therapy following registration, the subject must be taken off study in the CTMS (OnCore) with an appropriate date and reason entered.

4.2 **Registration Process for DF/HCC Institutions**

Applicable DF/HCC policy (REGIST-101) must be followed.

4.3 **General Guidelines for Other Investigative Sites**

Eligible participants will be entered on study centrally at DF/HCC by the Study Coordinator. Following registration, participants should begin protocol therapy within 7 days. Issues that would cause treatment delays should be discussed with the Sponsor-Investigator. If the subject does not receive protocol therapy following registration, the subject must be taken off study in the CTMS (OnCore) with an appropriate date and reason entered.

4.4 **Registration Process for Other Investigative Sites**

To register a participant, the following documents should be completed by the participating site and e-mailed to the Coordinating Coordinator:

- Current IRB approved informed consent document informed consent document signed by participant and investigator. Participant name and MRN must be redacted. Please ensure the participant's initials are written on each page of the informed consent document.
- HIPAA authorization form (if separate from the informed consent document)
- Signed and dated Eligibility Checklist
- The following source documentation is required:
    - Documentation of prior treatments/procedures performed to treat RCC
    - Reports documenting disease status
        - Chest CT
        - CT or MRI Abdomen and Pelvis
        - Tc^{99m} Bone Scan
    - Pathology Report
    - Concomitant medication list
    - Progress note or equivalent documentation of consenting visit
    - Progress note documenting medical history and oncologic history
    - Screening Labs
    - Screening visit note with vital signs, weight, height, ECOG performance status, physical examination

The participating site will then e-mail the Coordinating Coordinator to verify eligibility. The Study Coordinator will follow DF/HCC policy (REGIST-101) and register the participant on the protocol. The Study Coordinator will fax or e-mail the participant study number, and if applicable the dose treatment level, to the participating site. The Study Coordinator will also contact the participating site and verbally confirm registration.

5. TREATMENT PLAN

5.1. Treatment Regimen

Protocol treatment must start within 7 calendar days of enrollment. All study therapy will be administered on an outpatient basis. Unless otherwise specified, treatment delay of more than 28 days from date of last intended therapy will result in treatment discontinuation. For combination therapy regimens, a new cycle will not start until atezolizumab and/or abemaciclib are given. No minimum time interval is required between abemaciclib and atezolizumab administration. Vomited should be skipped, and abemaciclib dosing resumed at the next scheduled dose. If a dose is missed, it may be taken when remembered if there are at least 6 hours before the next scheduled dose. Held doses of atezolizumab or abemaciclib will be considered omitted for that cycle.

Table 1. ARM A Treatment

ARM A - Regimen Description					
	Prophylaxis Details & Precautions	**Starting Dose**	**Route**	**Schedule**	**Cycle Length**
Abemaciclib	Refer to *Table 20* for diarrhea supportive care and management guidance.	200mg BID	Oral	Days 1-21	21 Days

Table 3. ARM C Treatment

ARM C - Regimen Description Initial 5 patients					
	Prophylaxis Details & Precautions	**Starting Dose**	**Route[2]**	**Schedule**	**Cycle Length**

Atezolizumab	Consult with study PI regarding use of corticosteroids. G-CSF/GM-CSF is prohibited.	1200mg	IV over 60 (+/-5) minutes If the first infusion is tolerated, subsequent infusions may be administered over 30 (+/-5) minutes.	Day 1	21 Days
Subsequent 16 patients					
Abemaciclib	Refer to *Table 20* for diarrhea supportive care and management guidance.	200mg BID	Oral	Days 1-21	21 Days

[1]*Based on results of Bayesian toxicity monitoring, the starting dose of abemaciclib may be subsequently modified to a lower dose level.*
[2]*Infusion times may be extended as needed for safety (e.g., infusion reaction occurs). These instances must be documented in the patient medical records.*

Local intervention is discouraged unless medically unavoidable. Radiation therapy to the thorax (including to lungs/pleura, esophagus, intrathoracic lymph nodes, C7-L2 vertebrae, or ribs) is not permitted while on study and is strongly discouraged for at least 90 days after the last dose of abemaciclib and atezolizumab (whichever is later) unless for medical emergency such as impending spinal cord compression after approval in each individual case by Sponsor-Investigator. Palliative radiation to a symptomatic solitary lesion/area outside the thorax may be considered on a case-by-case basis and only after consultation with the Sponsor-Investigator. Subjects receiving local intervention (e.g., palliative radiation) are allowed to continue to receive study treatment at the treating investigator's discretion.

5.2. Pre-Treatment Criteria

Pre-treatment assessments should be performed within 72 hours of planned treatment dose. Results from the patient's complete blood counts and serum chemistry must be reviewed prior to drug dosing. Study agents must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol. Standard institutional procedures for administering an oral agent via by mouth will be followed. An adequate supply will be provided with instructions on home administration.

5.2.1. Cycle 1, Day 1

The patient's laboratory parameters must meet eligibility criteria (section 3.1.9) to initiate cycle 1 day 1 of trial therapy. Transfusion or growth factors are not permitted between screening up to and including cycle 1 day 1 to re-meet eligibility criteria except for

patients assigned to atezolizumab monotherapy in Arm C for whom red blood cell transfusion to meet eligibility criterion for hemoglobin is permitted.

5.2.2. Subsequent Cycles

Eligibility to receive subsequent doses is based on dose delay/modification criteria detailed in Section 6.

5.3. General Concomitant Medication and Supportive Care Guidelines

The treating investigator should discuss any questions regarding concomitant medications or treatments with the Sponsor-Investigator. The final decision on any supportive therapy or vaccination rests with the treating investigator. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the Sponsor-Investigator, treating investigator, and subject.

The following medications and treatments are <u>prohibited</u> while the patient is receiving protocol therapy:

- Any non-protocol antineoplastic therapy (radiation, chemo-, immuno- or biologic therapy)
- Other investigational agents
- Herbal products known to decrease PSA levels (e.g., Saw Palmetto, PC-SPES)
- Neulasta® and other granulocyte colony stimulating factors
- 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
- CYP3A inducers
- Systemic immunostimulatory agents (including, but not limited to, interferons and IL 2) are prohibited within 4 weeks or five drug elimination half-lives (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.
- Grapefruit or grapefruit juice
- 5 α-reductase inhibitors (e.g., finasteride, dutasteride)

For patients in Arms B and C only:

- Systemic glucocorticoids or other immunosuppressive drugs (for any purpose other than to modulate symptoms from a drug-related AE of immunologic etiology - Refer to Section 6 for applicable adjustment of protocol therapy).
- (If precluded by local regulations) live vaccines should not be given for 120 days after the last dose of checkpoint inhibitor immunotherapy is administered.

<u>NOTE:</u>

Use of strong CYP3A inhibitors is discouraged unless medically unavoidable. Introduction of treatment with a strong inhibitor may be considered on a case-by-case basis and only after consultation with the Sponsor-Investigator. *(use caution with moderate [e.g., ciprofloxacin] or weak [e.g., ranitidine] inhibitors).* Refer to Section 6.2 for dosing modification of abemaciclib.

The following medications and treatments are <u>permitted</u> while the patient is receiving protocol therapy:

- Ongoing androgen deprivation therapy (e.g., LHRH agonist/antagonist)
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)
- Megestrol acetate administered as an appetite stimulant
- Vaccinations (such as. influenza, SARS-CoV-2)
- Live, attenuated vaccines are not permitted
- Physiologic doses of prednisone ≤10 mg (or equivalent) per day
- Prophylactic corticosteroids to avoid allergic or other adverse reactions (e.g., known IV contrast allergy or prior to transfusions)
- Physiologic doses of corticosteroids (subject to discussion and approval of Sponsor-Investigator)
- Intermittent inhaled steroids or local injection of corticosteroids (subject to discussion and approval of Sponsor-Investigator)
- Bisphosphonates/RANKL inhibitors. Starting bisphosphonates while on study, if indicated, is also allowed.

5.4 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), treatment may continue indefinitely or until one of the following criteria applies:

- Disease progression by PCWG3 criteria (81), including clinical progression. Patients should not be discontinued from study therapy for PSA progression alone. PCWG3 criteria allow treatment beyond radiographic progression if the treating physician feels that the patient is continuing to derive clinical benefit from therapy, and the patient will continue until felt to be "no longer clinically benefiting" (NLCB). Patients in Arm B and the combination cohort of Arm C can be treated beyond progression per criteria in section 5.8.
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements

- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

When a participant is removed from protocol therapy and/or is off of the study, the participant's status must be updated in OnCore in accordance with REGIST-OP-1.

5.5 Duration of Follow Up

After treatment discontinuation, patients will be followed every 3 months for 24 months or until death, whichever occurs first. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event and for PSA and/or radiographic progression until a new treatment is started, the patient withdraws from study procedures, or death.

5.6 Criteria for Taking a Participant Off Study

Patients can be taken off study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation from study will be documented and may include:

- Development of second malignancy (except for basal cell carcinoma or squamous cell carcinoma of the skin) that requires treatment, which would interfere with this study;
- Patient withdraws consent (termination of treatment AND follow-up);
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment;
- Physician discretion (e.g., noncompliance or other circumstance);
- Lost to Follow-up;
- Termination of the study by Sponsor-Investigator or FDA;
- Patient completes protocol treatment and follow-up criteria.
- Death

Document in the source the reason for ending protocol therapy and the date the patient was removed from treatment. All patients who discontinue treatment should comply with protocol specific follow-up procedures as outlined in Section 10. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability

to consent freely.

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF). In addition, the study team will ensure the participant's status is updated in OnCore in accordance with REGIST-OP-1.

5.7 Patient Replacement

Patients who have been registered and receive no protocol therapy will be replaced.

Patients who receive local intervention (e.g., palliative radiation) may be considered not evaluable These patients may subsequently be assigned a conservative censoring or progression date.

5.8 Treatment Beyond Progression

Accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of PD.

Subjects treated in C will be permitted to continue study treatment beyond initial RECISTv1.1 defined PD, assessed by the investigator, as long as they meet the following criteria:

- Investigator determined clinical benefit
- Tolerance of study drug
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (e.g., CNS metastases)

6. DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made as indicated in the following table(s). The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Any patient who receives protocol treatment will be evaluable for toxicity. Each patient will be assessed for the development of toxicity according to the Study Calendar (Section 10). Toxicity will be assessed according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. Dose adjustments should be made according to the system showing the greatest degree of toxicity. The dose delays and modifications described here are requirements, but re-escalation of abemaciclib dose is permitted per discretion of the treating investigator if there is improvement in the adverse event for which the dose was initially reduced. Investigators are encouraged to contact the Sponsor-Investigative team with any questions.

Table 4. Abemaciclib Dosing Modifications

Abemaciclib Dosing Modifications		
Dose Level	**Monotherapy**	**Combination therapy**
1	200mg BID	150mg BID
-1	150mg BID	100mg BID
-2	100mg BID	50mg BID
-3	50mg BID	Discontinue

6.1 Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

Toxicities associated or possibly associated with atezolizumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, should be used to evaluate for a possible immunogenic etiology.

Although most immune-mediated adverse events observed with atezolizumab have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of atezolizumab may not have an immediate therapeutic effect, and in severe cases, immune-related toxicities may require acute management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents.

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

- Patients and family caregivers should receive timely and up-to-date information about immunotherapies, their mechanism of action, and the clinical profile of possible immune-related adverse events prior to initiating therapy and throughout treatment and survival follow-up. There should be a high level of suspicion that new symptoms are treatment related.
- In general, atezolizumab therapy should be continued with close monitoring for Grade 1 toxicities, with the exception of some neurologic toxicities.
- Consider holding atezolizumab for most Grade 2 toxicities and resume when symptoms and/or laboratory values resolve to Grade 1 or better. Corticosteroids (initial dose of 0.5-1 mg/kg/day of prednisone or equivalent) may be administered.
- For Grade 2 recurrent or persistent (lasting for more than 5 days) events, treat as a Grade 3 event.
- Hold atezolizumab for Grade 3 toxicities and initiate treatment with high-dose corticosteroids (1-2 mg/kg/day prednisone or equivalent). Corticosteroids should be tapered over 1 month to 10 mg/day oral prednisone or equivalent, before atezolizumab can be resumed. If symptoms do not improve within 48 to 72 hours of high-dose corticosteroid use, other immunosuppressants may be offered for some toxicities.
- In general, Grade 4 toxicities warrant permanent discontinuation of atezolizumab treatment, with the exception of endocrinopathies that are controlled by hormone replacement therapy.

The investigator should consider the benefit–risk balance for a given patient prior to further administration of atezolizumab. In patients who have met the criteria for permanent discontinuation, resumption of atezolizumab may be considered if the patient is deriving benefit and has 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.

DOSE MODIFICATIONS

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

TREATMENT INTERRUPTION

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed. If atezolizumab is withheld for > 12 weeks after event onset, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for > 12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for > 12 weeks if the patient is likely to derive clinical benefit. The decision to re–challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption 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.

PULMONARY EVENTS

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 in Table 5.

Table 5. Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
Pulmonary Event, Grade 1	• Continue atezolizumab and monitor closely. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist. • For Grade 1 pneumonitis, consider withholding atezolizumab.
Pulmonary Event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. • 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] • For recurrent events, or 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 abemaciclib and atezolizumab and contact Sponsor-Investigator. • Oral or IV broad-spectrum antibiotics should be administered in parallel to the immunosuppressive treatment. • Bronchoscopy or BAL 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.

BAL = bronchoscopic alveolar lavage.[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).

GASTROINTESTINAL EVENTS

Immune-mediated colitis has been associated with the administration of atezolizumab. Management guidelines for diarrhea or colitis are provided in **Error! Reference source not found.**6.

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.

Table 6. Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis)

Event	Management
Diarrhea or colitis, Grade 1	• Continue atezolizumab. • Initiate symptomatic treatment. • Endoscopy is recommended if symptoms persist for > 7 days. • Monitor closely.
Diarrhea or colitis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate symptomatic treatment. • Patient referral to GI specialist is recommended. • For recurrent events or events that persist > 5 days, initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone. If the 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-Investigator. [c]
Diarrhea or colitis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist for evaluation and confirmatory biopsy. • 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 the 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-Investigator. [c] •
Grade 4	• Permanently discontinue atezolizumab and contact Sponsor-Investigator. [c] • Refer patient to GIspecialist for evaluation and confirmation biopsy. • Initiate treatment with 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 of 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 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-related event. The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit-risk and documented by both the investigator (or an appropriate delegate) and the Sponsor-Investigator.

ENDOCRINE EVENTS

Management guidelines for endocrine events are provided in Table 7.

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.

Table 7. Management Guidelines for Endocrine Events

Event	**Management**
Grade 1 Hypothyroidism	• Continue atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely.
Grade 2 Hypothyroidism	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving.
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. • Monitor TSH every 4 weeks. • Consider patient referral to endocrinologist. TSH < 0.1 mU/L: • Follow guidelines for symptomatic hyperthyroidism. • Consider patient referral to endocrinologist.

Grade 2 hyperthyroidism	• Consider withholding atezolizumab. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled, and thyroid function is improving.
Grade 3 and 4 Hyperthyroidism	• Withhold atezolizumab. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab and contact *Sponsor-Investigator* for life-threatening immune-related hyperthyroidism. [c]
Symptomatic Adrenal Insufficiency, Grades 2-4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Consider patient referral to endocrinologist. • Perform appropriate imaging. • 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 and patient is stable on replacement therapy, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab and contact Sponsor-Investigator. [c]
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.
Hyperglycemia Grade 3 or 4	• Withhold atezolizumab. • Initial treatment with insulin. • Evaluate for diabetic ketoacidosis and manage as per institutional guidelines. • Monitor for glucose control • Resume atezolizumab when symptoms resolve and glucose levels are stable. • For recurrent Grade 3 or higher events, permanently discontinue atezolizumab and contact Sponsor-Investigator. [c]
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Consider patient referral to endocrinologist. • Perform brain MRI (pituitary protocol). • 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. [a] • Initiate hormone replacement if clinically indicated. • 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-Investigator. [c] • For recurrent hypophysitis, treat as Grade 4 event.
Hypophysitis (pan-hypopituitarism), Grade 4	• Permanently discontinue atezolizumab and contact Sponsor-Investigator. [c] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol).

	• 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. [a] • Initiate hormone replacement if clinically indicated.

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.
[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-related event. The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by both the investigator (or an appropriate delegate) and the Sponsor-Investigator.

OCULAR EVENTS

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). Management guidelines for ocular events are provided in **Error! Reference source not found.**.

Table 8. Management Guidelines for Ocular Events

Event	Management
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 and contact Sponsor-Investigator. [c]
Ocular Event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Sponsor-Investigator. [c] • Refer patient to ophthalmologist. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV oral prednisone. • 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-related event. The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by both the investigator (or an appropriate delegate) and the Sponsor-Investigator.

IMMUNE-MEDIATED CARDIAC EVENTS

IMMUNE-MEDIATED MYOCARDITIS

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 or associated with pericarditis (see section on pericardial disorders below) 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 in **Error! Reference source not found.**9.

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 in

Table 9. Withhold treatment with atezolizumab for Grade 1 pericarditis and conduct a detailed cardiac evaluation to determine the etiology and manage accordingly.

Table 9. Management Guidelines for Immune-Mediated Myocarditis and Pericardial Disorders

Event	Management
Immune-mediated myocarditis, Grades 2-4 Immune-mediated pericardial disorders, Grades 2-4	• Permanently discontinue atezolizumab. and contact Sponsor-Investigator. • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • 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.

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

INFUSION-RELATED REACTIONS AND CYTOKINE-RELEASE SYNDROME

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

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

CRS is defined as a supraphysiologic response following administration of any immune therapy that results in activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, always include fever at the onset, and may include hypotension, capillary leak (hypoxia), and end-organ dysfunction (83). 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 (84, 85), including atezolizumab.

There may be significant overlap in signs and symptoms of IRRs and CRS, and in recognition of the challenges in clinically distinguishing between the two, consolidated guidelines for medical management of IRRs and CRS are provided in Table 10.

Severe COVID-19 appears to be associated with a CRS involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and IFN-γ (86). 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.

Table 10. Management Guidelines for Infusion-related Reactions and Cytokine Release Syndrome

Event	Management
Grade 1 [a] Fever [b] with or without constitutional symptoms	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment, [c] including maintenance of IV fluids for hydration. • In case of rapid decline or prolonged CRS (> 2 days) or in patients with significant symptoms and/or comorbidities, consider managing as per Grade 2. • For subsequent infusions, consider administration of oral premedication with antihistamines, 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 closely (in the ICU, if appropriate). Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Consider IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. • Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize patient (monitoring in the ICU is recommended), permanently discontinue atezolizumab. [e] • If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab may be administered. For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for IRRs and/or CRS. • If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact the Sponsor-Investigator.
Grade 3 [a] Fever [b] with hypotension requiring a vasopressor (with or without vasopressin) **and/or** Hypoxia requiring high-flow oxygen [d] by nasal cannula, face mask, non-rebreather mask, or Venturi mask	• Permanently discontinue atezolizumab and contact Sponsor-Investigator. [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 as described in this appendix. • 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.
Grade 4 [a]	• Permanently discontinue atezolizumab and contact Sponsor-Investigator. [e] • Administer symptomatic treatment. [c]

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)	• 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 as described in this appendix. • 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. • Hospitalize patient until complete resolution of symptoms.

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

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

[a] Grading system for these management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE v5.0 should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.

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

[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 immune-related event. The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by both the investigator (or an appropriate delegate) and the Sponsor-Investigator. 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 assessing the benefit–risk ratio.

[f] Refer to Riegler et al. (87).

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 in Table 11.

Table 11. Management Guidelines for Pancreatic Events, Including Pancreatitis

Amylase and/or lipase elevation	Management
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 event.
Amylase and/or lipase elevation, Grade 3 or 4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Consider patient referral 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 Sponsor-Investigator. [c] • For recurrent events, permanently discontinue atezolizumab and contact Sponsor-Investigator. [c]
Immune-mediated pancreatitis, Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Consider patient referral 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 Sponsor-Investigator. [c] • For recurrent events, permanently discontinue atezolizumab and contact Sponsor-Investigator. [c]
Immune-mediated pancreatitis, Grade 4	• Permanently discontinue atezolizumab and contact Sponsor-Investigator. [c] • Refer patient to specialist. • Initiate treatment with 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 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-related event. The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by both the investigator (or an appropriate delegate) and the Sponsor-Investigator.

DERMATOLOGIC EVENTS

Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash were mild in severity and self-limiting, with or without pruritus. Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in Table 12.

Table 12. Management Guidelines for Dermatologic Events

Event	Management
Dermatologic event, Grade 1	• Continue atezolizumab • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	• Continue atezolizumab. • Consider patient referral to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve. • If unresponsive to topical corticosteroids, consider oral prednisone 0.5 mg/kg/day.
Dermatologic event, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patients to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with corticosteroids equivalent to 10 mg/day oral prednisone, 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-Investigator. [c]
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and contact Sponsor-Investigator. [c]
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	**Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis:** • Withhold atezolizumab for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis. • Confirm diagnosis by referring 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 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 ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.
[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by both the investigator (or an appropriate delegate) and the Sponsor-Investigator.

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 in Table 13.

Table 13. Management Guidelines for Neurologic Disorders

Event	Management
Immune-mediated neuropathy, Grade 1	• Continue atezolizumab. • Investigate etiology. • Any cranial nerve disorder (including facial paresis) should be managed as per Grade 2 management guidelines below.
Immune-mediated neuropathy, including facial paresis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Investigate etiology and consider patient referral 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] •
Immune-mediated neuropathy, including facial paresis, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Sponsor-Investigator. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines.
Myasthenia gravis or Guillain Barre syndrome (any grade)	• Permanently discontinue atezolizumab and contact Sponsor-Investigator. [c] • Refer patient to neurologist. • Initiate treatment per institutional guidelines. • Consider initiation of 1-2 mg/kg/day oral or IV prednisone.

[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-related event. The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by both the investigator (or an appropriate delegate) and the Sponsor-Investigator.

Table 14. 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.

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 in Table 15.

Table 15. Management Guidelines for Immune-mediated meningoencephalitis

Event	Management
Immune-mediated meningoencephalitis, all grades	• Permanently discontinue atezolizumab and contact Sponsor-Investigator. [c] • Refer patient to neurologist. • Initiate treatment with corticosteroids equivalent to 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] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to rechallenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by both the investigator (or an appropriate delegate) and the Sponsor-Investigator.

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 in Table 16.

Table 16. Management Guidelines for Renal Events

Event	Management
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] • Consider patient referral 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-Investigator. [c]
Renal event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Sponsor-Investigator. [c] • 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 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-related event. The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit-risk and documented by both the investigator (or an appropriate delegate) and the Sponsor-Investigator.

HEPATIC EVENTS

Immune-mediated hepatitis has been associated with the administration of atezolizumab. Patients eligible for study treatment 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 **Error! Reference source not found.**17.

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.

Table 17. Management Guidelines for Hepatic Events

Event	Management
Hepatic event, Grade 1	• Continue atezolizumab. • Monitor LFTs until values resolve to within normal limits or to baseline values.
Hepatic event, Grade 2	**All events:** • Monitor LFTs more frequently until return to baseline values. **Events of > 5 days' duration:** • Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone. • 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-Investigator. [c]
Hepatic event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Sponsor-Investigator. [c] • Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • 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.

LFT = liver function test.
[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-related event. The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by both the investigator (or an appropriate delegate) and the sponsor-investigator.

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 in Table 8.

Table 18 Management Guidelines for Immune-Mediated Myositis

Event	Management
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. [c]

Immune-mediated myositis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • 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. [c] • For recurrent events, treat as a Grade 4 event.
Immune-mediated myositis, Grade 4	• Permanently discontinue atezolizumab. [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 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).

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AND MACROPHAGE ACTIVATION SYNDROME

Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS), which are considered to be potential risks for atezolizumab.

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 (88). A patient should be classified as having HLH if five of the following eight criteria are met:

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

Patients with suspected MAS should be diagnosed according to published criteria for systemic juvenile idiopathic arthritis by Ravelli et al. (89). A febrile patient should be classified as having MAS if the following criteria are met:

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

Patients with suspected HLH or MAS should be treated according to the guidelines in Table 9.

Table 19 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome

Event	Management
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 according to published guidelines (90-92). • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

HLH = hemophagocytic lymphohistiocytosis; MAS = macrophage activation syndrome.

6.2 Abemaciclib Toxicity Management

Table 20. Diarrhea

Diarrhea	Management
(management overview)	Clinical trial data indicates the majority of patients who receive abemaciclib will develop diarrhea. Our experience indicates early identification and intervention for the management of diarrhea has been helpful to patients. At time of enrollment, patients should receive instructions on the prompt management of diarrhea. In the event of diarrhea, supportive care measures should be initiated as early as possible. These include the following: At the first sign of loose stools, the patient should initiate antidiarrheal therapy (e.g., loperamide) and notify the investigator for further instructions and appropriate follow-up. Patients should also be encouraged to drink fluids (e.g., 8 to 10 glasses of clear liquids per day). Site personnel should assess response within 24 hours.
Grade 1	Dose modification not required.
Grade 2	If toxicity does not resolve within 24 hours to ≤ Grade 1, suspend dose until resolution. Dose reduction not required.
Grade 2 *that persists or recurs after resuming the same dose despite maximal supportive measures*	Suspend dose until toxicity resolves to ≤ Grade 1. Resume at next lower dose.
Grade 3 or 4, or requiring hospitalization	

Table 21. Interstitial lung disease (ILD) or Pneumonitis Events

Interstitial lung disease (ILD) or Pneumonitis Events	Management
(management overview)	Interstitial lung disease (ILD) / pneumonitis has been identified as an adverse drug reaction for abemaciclib. Adverse events reported included events such as interstitial lung disease, pneumonitis, obliterative bronchiolitis, organizing pneumonia, pulmonary fibrosis. The majority of events were Grade 1 or Grade 2 with serious cases and fatal events reported. Patients should be asked to report any new or worsening pulmonary symptoms such as dyspnea, cough and fever; these symptoms should be investigated and treated as per local clinical practice and/or guidelines (including corticosteroids as appropriate). Investigations may include imaging such as high resolution computer tomography (HRCT), bronchoalveolar lavage (BAL), and biopsy as clinically indicated.
Grade 1, development of radiological or PFT changes suggestive of pneumonitis and have few or no symptoms	• Perform high-resolution CT scan (defined as slice thickness of 1 to 1.25mm and use of high special frequency algorithm). • If after initial workup, the patient does not meet CTCAE 5.0 criteria for grade >=2 pneumonitis/ILD (symptomatic or needing medical intervention), treatment may be continued • The patient will be monitored closely with high-resolution CT scans and PFTs every 8 weeks until resolution of Grade 1 pneumonitis or until worsening to grade >=2 pneumonitis/ILD at which time the treatment must be withheld per protocol. • Consider patient referral to pulmonary specialist.
Grade 2, 3 or 4	• Permanently discontinue abemaciclib and atezolizumab and contact Sponsor-Investigator. • Referral to pulmonary specialist is recommended with consideration of bronchoscopy or BAL. • Initiate treatment with 1-2 mg/kg/day oral prednisone or equivalent. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month. • Patients who develop >= grade 2 pneumonitis/ILD must withdraw from further study treatment

Table 22. ALT or AST Increase

ALT or AST increase	Management
Grade 1 (ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal) or Grade 2 (>3.0 - 5.0 x ULN if baseline was	Dose modification not required.

<table>
<tr><td>normal; >3.0 - 5.0 x baseline if baseline was abnormal)</td><td></td></tr>
<tr><td>Transient Grade 2</td><td>Liver testing, including ALT, AST, ALP, total bilirubin, direct bilirubin, gamma-glutamyl transferase, and creatine kinase, should be repeated within 2 to 4 days to confirm the abnormality and to determine if it is increasing or decreasing.</td></tr>
<tr><td>Persistent or Recurrent Grade 2 that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1, or Grade 3</td><td>Suspend dose until toxicity resolves to baseline or Grade 1. Resume at next lower dose.

If the abnormality persists or worsens, clinical and laboratory monitoring and evaluation for possible causes of abnormal liver tests, should be initiated by the investigator. At a minimum, this evaluation should include physical examination and a thorough medical history, including symptoms, recent illnesses (for example, heart failure, systemic infection, hypotension, or seizures), history of concomitant medications (including over-the-counter, herbal and dietary supplements, history of alcohol drinking and other substance abuse). In addition, the evaluation should include a blood test for prothrombin time (PT-INR); serological tests for viral hepatitis A, B, C, E, autoimmune hepatitis; and an abdominal imaging study (for example, ultrasound or CT scan).

Based on the patient's history and initial evaluation results, further testing should be considered in consultation with the Sponsor-Investigator, including tests for hepatitis D virus (HDV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and serum phosphatidylethanol, as well as additional laboratory testing from the list below as indicated based on the patient's medical history, risk factors and exposures. Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a hepatologist or gastroenterologist consultation, magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), cardiac echocardiogram, and/or a liver biopsy:

<table>
<tr><td>Hematology</td><td>Clinical Chemistry</td></tr>
<tr><td>Hemoglobin</td><td>Total bilirubin</td></tr>
<tr><td>Hematocrit</td><td>Direct bilirubin</td></tr>
<tr><td>Erythrocytes (RBCs - red blood cells)</td><td>Alkaline phosphatase (ALP)</td></tr>
<tr><td>Leukocytes (WBCs - white blood cells)</td><td>Alanine aminotransferase (ALT)</td></tr>
<tr><td>Differential:</td><td>Aspartate aminotransferase (AST)</td></tr>
<tr><td>Neutrophils, segmented</td><td>Gamma-glutamyl transferase (GGT)</td></tr>
<tr><td>Lymphocytes</td><td>Creatine kinase (CK)</td></tr>
<tr><td>Monocytes</td><td>Other Chemistry</td></tr>
<tr><td>Basophils</td><td>Acetaminophen</td></tr>
<tr><td>Eosinophils</td><td>Acetaminophen protein adducts</td></tr>
<tr><td>Platelets</td><td>Alkaline phosphatase isoenzymes</td></tr>
<tr><td>Cell morphology (RBC and WBC)</td><td>Ceruloplasmin</td></tr>
<tr><td rowspan="2">Coagulation</td><td>Copper</td></tr>
<tr><td>Ethyl alcohol (EtOH)</td></tr>
</table>
</td></tr>
</table>

	Prothrombin time, INR (PT-INR)	Haptoglobin
	Serology	Immunoglobulin IgA (quantitative)
	Hepatitis A virus (HAV) testing:	Immunoglobulin IgG (quantitative)
	HAV total antibody	Immunoglobulin IgM (quantitative)
	HAV IgM antibody	Phosphatidylethanol (PEth)
	Hepatis B virus (HBV) testing:	**Urine Chemistry**
	Hepatitis B surface antigen (HBsAg)	Drug screen
	Hepatitis B surface antibody (anti-HBs)	Ethyl glucuronide (EtG)
	Hepatitis B core total antibody (anti-HBc)	**Other Serology**
	Hepatitis B core IgM antibody	Anti-nuclear antibody (ANA)
	Hepatitis B core IgG antibody	Anti-smooth muscle antibody (ASMA)
	HBV DNA	Anti-actin antibody
	Hepatis C virus (HCV) testing:	Epstein-Barr virus (EBV) testing:
	HCV antibody	EBV antibody
	HCV RNA	EBV DNA
	Hepatitis D virus (HDV) testing:	Cytomegalovirus (CMV) testing:
	HDV antibody	CMV antibody
	Hepatitis E virus (HEV) testing:	CMV DNA
	HEV IgG antibody	Herpes simplex virus (HSV) testing:
	HEV IgM antibody	HSV (Type 1 and 2) antibody
	HEV RNA	HSV (Type 1 and 2) DNA
	Microbiology	Liver kidney microsomal type 1 (LKM-1) antibody
	Culture:	-
	Blood	-
	Urine	-
Grade 2 or 3 (>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal) with total bilirubin >2 x ULN, in the absence of	Discontinue abemaciclib and contact Sponsor-Investigator.	

cholestasis OR Grade 4 (>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal)	

Table 23. Hematologic Toxicity

Hematologic Toxicity	Management
(management overview)	Hematologic toxicities including neutropenia, leukopenia, anemia, and thrombocytopenia have been observed in patients treated with abemaciclib, and causality has been established. Severe (Grade 3 and 4) neutropenia was observed in patients receiving abemaciclib. Patients should be monitored closely for signs of infection, anemia, and bleeding.
Grade 1 or 2	Dose modification not required.
Grade 3	Suspend dose until toxicity resolves to ≤Grade 2. Dose modification not required.
Grade 3, recurrent or Grade 4	Suspend dose until toxicity resolves to ≤Grade 2. Resume at next lower dose.
Requiring administration of blood cell growth factor	Suspend abemaciclib dose for at least 48 hours after the last dose of blood cell growth factor and until toxicity resolves to ≤Grade 2. Resume abemaciclib at next lower dose unless the dose was already reduced for the toxicity that led to the use of the growth factor.

Table 24. Non-Hematologic Toxicity

Non-Hematologic Toxicity (excluding diarrhea, hepatotoxicity, and ILD/pneumonitis)	Management
Grade 1 or 2	Dose modification not required.
Persistent or recurrent Grade 2 toxicity that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Suspend dose until toxicity resolves to baseline or Grade 1. Resume at next lower dose.
Grade 3 or 4	Suspend dose until toxicity resolves to baseline or Grade 1. Resume at next lower dose.

6.2.1 Condition requiring introduction (unavoidable) of treatment with strong CYP3A inhibitor

Introduction of strong CYP3A inhibitor is subject to discussion and approval of Sponsor-Investigator For all but ketoconazole, reduce abemaciclib to 100 mg BID. In the case of ketoconazole, reduce abemaciclib to 50 mg BID. For patients who have had dose reduction to 100 mg BID due adverse events, dose will be further reduced to 50 mg BID. Subsequently, if the CYP3A inhibitor is discontinued, increase abemaciclib dose (after inhibitor 3-5 half-lives) to the dose that was given prior to starting the inhibitor.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

7.1 Expected Toxicities

7.1.1 Abemaciclib

Most common adverse reactions (incidence ≥20%) are diarrhea, neutropenia, nausea, abdominal pain, infections, fatigue, anemia, leukopenia, decreased appetite, vomiting, headache, alopecia, and thrombocytopenia.

Increases in Serum Creatinine and Renal Insufficiency:
Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular transporters without affecting glomerular function (as measured by iohexol clearance). In clinical studies, increases in serum creatinine occurred within the first month of abemaciclib dosing, remained elevated but stable through the treatment period, were reversible upon treatment discontinuation, and were not accompanied by changes in markers of renal function, such as blood urea nitrogen (BUN), cystatin C, or calculated glomerular filtration rate based on cystatin C.

7.1.2 Atezolizumab

Most common adverse reactions (≥ 20%) in patients with locally advanced or metastatic urothelial carcinoma were fatigue, decreased appetite, nausea, constipation, urinary tract infection, diarrhea, and pyrexia. Most common adverse reactions (≥ 20%) in patients with metastatic non-small cell lung cancer were fatigue, decreased appetite, dyspnea and cough.

Atezolizumab has been associated with risks such as the following: IRRs and immune-mediated 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. In addition, 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. Refer to Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

7.2 Adverse Event Characteristics and Definitions

7.2.1 **Adverse Events**

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding),

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 prostate cancer 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.

7.2.2 **Serious Adverse Events**

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

- It results in death (i.e., the AE actually 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.
- 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).

7.2.3 **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 the FDA, appropriate IRB(s), and Genentech, Inc. in accordance with CFR 312.32 (IND Safety Reports).

7.2.4 **Adverse Event Reporting Period**

The study period during which AEs and SAEs, where the patient has been exposed to atezolizumab and/or abemaciclib must be reported. Reporting period begins after informed consent is obtained and initiation of study treatment and ends 30 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment.

7.2.5 **Assessment of Severity of Adverse Events**

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found

in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

The below table should be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 25. Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated d
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 (v5.0), 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, managing money, etc.

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

c. If an event is assessed as a "significant medical event," it must be reported as a serious adverse event

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

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
  - Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

7.2.6 **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 atezolizumab and/or abemaciclib, and actions taken.

- **Attribution** of the AE:
- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unlikely – The AE *is doubtfully related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

Yes: Related (definite, probable, possible)

There is a plausible temporal relationship between the onset of the AE and administration of the atezolizumab and/or abemaciclib 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 and/or abemaciclib or with similar treatments; and/or the AE abates or resolves upon discontinuation of the atezolizumab and/or abemaciclib or dose reduction and, if applicable, reappears upon re- challenge.

No: Not Related (unlikely, unrelated)

Evidence exists that the AE has an etiology other than the atezolizumab and/or abemaciclib (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to atezolizumab and/or abemaciclib 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 Investigator Brochure (I.B).

Unexpected adverse events are those not listed in the P.I or current I.B or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis.

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

7.2.7 **Procedures For Eliciting, Recording, And Reporting Adverse Events**

7.2.7.1 **Eliciting Adverse Events**

A consistent methodology for eliciting AEs at all subject evaluation time points should be adopted. Examples of non-directive questions include:

- "How have you felt since your last clinical visit?"
- "Have you had any new or changed health problems since you were last here?"

7.2.7.2 **Specific Instructions for Recording Adverse Events**

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

Infusion-Related Reactions and Cytokine-Release Syndrome

There may be significant overlap in signs and symptoms of IRRs and cytokine-release syndrome (CRS). While IRRs occur during or within 24 hours after treatment administration, time to onset of CRS may vary. Differential diagnosis should be applied, particularly for late-onset CRS (occurring more than 24 hours after treatment administration), to rule out other etiologies such as delayed hypersensitivity reactions, sepsis or infections, HLH, tumor lysis syndrome, early disease progression, or other manifestations of systemic inflammation.

Adverse events that occur during or within 24 hours after study treatment administration and are judged to be related to study treatment infusion should be captured on the Adverse Event eCRF as a diagnosis (e.g., "infusion-related reaction" or "cytokine release syndrome"). Avoid ambiguous terms such as "systemic reaction." Cases of late-onset CRS should be reported as "cytokine-release syndrome" on the Adverse Event eCRF. Associated signs and symptoms of an IRR should be recorded on the dedicated Infusion-Related Reaction eCRF.
If a patient experiences both a local and systemic reaction to a single administration of study treatment, each reaction should be recorded separately on the Adverse Event eCRF, with associated signs and symptoms of an IRR also recorded separately on the dedicated Infusion-Related Reaction eCRF.

In recognition of the challenges in clinically distinguishing between IRRs and CRS, consolidated guidelines for medical management of IRRs and CRS are provided in Section 6.1 "Infusion-Related Reactions and Cytokine-Release Syndrome."

7.2.7.3 **Diagnosis vs. 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.

7.2.7.4 **Deaths**

All deaths that occur during the protocol-specified AE reporting period (see Section 7.2.4), 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".

7.2.7.5 **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").

Lack of Efficacy or Worsening of Underlying Cancer
Deterioration that is judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature (i.e., deterioration beyond the expected pattern of progression of the underlying disease) should be recorded as an adverse event. When recording an unanticipated worsening of underlying cancer on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated worsening of prostate cancer"). Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on PCWG3 criteria. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

7.2.7.6 **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 as a result 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

7.2.8 **Adverse Event of Special Interest (AESI) for Atezolizumab**

AESIs are a subset of adverse events which may be of scientific and medical concern specific to the study drug, for which ongoing monitoring and expedited communication 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.

AESIs applicable to all participants in this trial are:

- Cases of potential drug-induced liver injury (DILI) that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law:
    - Treatment-emergent ALT or AST > 3× ULN in combination with total bilirubin > 2× ULN
    - Treatment-emergent ALT or AST > 3× ULN in combination with clinical jaundice
- Suspected transmission of an infectious agent by the study drug (STIAMP), as defined below:
  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- ILD/Pneumonitis

AESIs associated with participants receiving Atezolizumab:

- Systemic lupus erythematosus
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine release syndrome, macrophage activating syndrome and hemophagocytic lymphohistiocytosis syndrome
- 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

7.2.9 **Other Special Situations**

The following other Special Situations Reports should be collected even in the absence of an Adverse Event and transmitted to Genentech:

- 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

Pregnancy
Such events include pregnancy (occurring in the partner of the male study subject), where the fetus may have been exposed to the study drug (conception while the study subject was receiving protocol therapy or within 5 months after the last dose of study drug); data related to the Product usage during breastfeeding; study drug interaction; study drug overdose, abuse or 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

NOTE: Abortions, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the study drug should be reported as an SAE.

7.2.10 **Product complaints**

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.

7.2.11 **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 and/or abemaciclib exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject [including pregnancy occurring in the partner of a male study subject] who participated in the study, this should be reported as an SAE adequately to Genentech drug Safety during follow up period.

7.3 Dose-Limiting Toxicities (DLT)

A DLT will be defined as any of the following treatment-related events at any point during drug dosing:

Hematologic Toxicity

- Grade 3 thrombocytopenia associated with clinically significant bleeding and requiring platelet transfusion

- Grade 4 thrombocytopenia
- Grade ≥3 febrile neutropenia
- Grade ≥3 anemia requiring a blood transfusion
- Other Grade 4 toxicity lasting >7 days

Non-Hematologic Toxicity

- Grade ≥3 fatigue lasting >7 days
- Grade ≥3 nausea, vomiting, and diarrhea lasting >3 days despite optimal medical management
- Grade ≥3 hypertension despite maximal medical therapy
- Grade 2 pneumonitis that does not resolve to Grade ≤1 within 14 days after initiation of optimal medical management including corticosteroid therapy
- Grade ≥3 colitis or noninfectious pneumonitis
- Grade 3 irAE* (excluding colitis or pneumonitis) that:
    - does not downgrade to Grade 2 within 14 days after onset of the event despite optimal medical management
      or
    - does not downgrade to Grade ≤1 or the patient's baseline level within 30 days of event onset
- Grade 4 irAE*

Other Toxicity

- ALT or AST:
    - >8 × ULN, if the patient does not have HCC or liver metastasis
      or
    - ≥2-fold above the patient's baseline value that lasts >7 days, if the patient has HCC or liver metastasis and had ALT or AST >3.0 × ULN at baseline
      or
    - >3 × ULN with concomitant bilirubin >2 × ULN, in the absence of cholestasis
- Grade 3 bilirubin (total) level
- Grade 3 or 4 amylase or lipase that does not resolve to Grade ≤2 within 7 days of starting IV corticosteroid therapy
- Other Grade 3 or 4 laboratory value lasting >14 days or requiring medical intervention
- Grade 5 toxicity (i.e. event that results in death)
- Toxicity otherwise deemed by the treating and/or Sponsor Investigator to be dose limiting (e.g., toxicity that is possibly related to study treatment and requires treatment discontinuation prior to completion of Cycle 1; persistent Grade >2 toxicities causing a delay of >14 days in initiating Cycle 2)

*irAE=immune-related Adverse Event (i.e. an Adverse Event consistent with an immune-mediated mechanism of action with no clear alternate etiology

7.3.1 Events not considered to be a Dose-Limiting Toxicity

Hematologic Toxicity

- Grade 3 or 4 neutropenia if:
  not associated with fever or systemic infection
  and
  improves by at least 1 grade within 7 days
- Grade 3 or 4 lymphopenia

Other Toxicity

- Grade 3 infusion-related reaction during infusion of atezolizumab, if:
  the patient did not receive corticosteroid prophylaxis
  and
  the Grade 3 reaction resolves (with appropriate clinical management) within 6 h
- Isolated Grade 3 electrolyte abnormalities if:
  not associated with clinical signs or symptoms
  and
  reversed with appropriate maximal medical intervention within 2 days
- Vitiligo or alopecia (any grade)
- Grade 3 endocrine disorder (thyroid, pituitary, and/or adrenal insufficiency), if:
  the disorder is manageable with or without systemic corticosteroid therapy and/or hormone replacement therapy
  and
  the patient is asymptomatic
- Grade 3 inflammatory reaction attributed to a local antitumor response (such as, inflammatory reaction in the lymph nodes or at sites of metastatic disease)
- Toxicity that is clearly and directly related to the primary disease or to another etiology

7.4 Adverse Event Reporting

7.4.1 In the event of an unanticipated problem or life-threatening complications treating investigators must immediately notify the PI.

7.4.2 Investigators **must** report to the PI any adverse event (AE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment. Serious adverse events should be reported per the guidelines in Table 26 on the MedWatch Adverse Event Reporting form.

7.4.3 Adverse Event Reporting Guidelines

All participating sites will report AEs to the Sponsor-Investigator per DF/HCC

requirements, and the IRB of record for each site as applicable per IRB policies. The table below indicates which events must be reported to the DF/HCC Sponsor-Investigator.

Table 26. DF/HCC Reportable Adverse Events(AEs)

Attribution	DF/HCC Reportable Adverse Events(AEs)				
	Gr. 2 & 3 AE Expected	**Gr. 2 & 3 AE Unexpected**	**Gr. 4 AE Expected**	**Gr. 4 AE Unexpected**	**Gr. 5 AE Expected or Unexpected**
Unrelated Unlikely	Not required	Not required	5 calendar days#	5 calendar days	24 hours*
Possible Probable Definite	Not required	5 calendar days	5 calendar days#	5 calendar days	24 hours*
# If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported.					
* For participants enrolled and actively participating in the study ***or*** for AEs occurring within 30 days of the last intervention, events must be reported within 1 business day of learning of the event.					

7.5 Reporting procedures to Eli Lilly

The following are required for IIT Protocols to comply with applicable laws, regulations and standards regarding Investigator's and Institution's obligations, as the sponsor of the Study, to collect and report adverse events to regulatory authorities, IRBs, Ethics Committees or other third parties:

In addition to the obligations set forth below, Investigator and Institution agree to provide Lilly with a copy of all information Investigator and/or Institution submit to regulators related to any adverse events for the Study Drug that occur during the Study that Investigator and/or Institution have not otherwise provided Lilly; to notify Lilly, sub-investigators, and the IRB of any problems involving risk to Study patients and report new safety information to IRBs in accordance with applicable requirements; to notify Lilly within fifteen (15) business days of Investigator and/or Institution receiving notification of any "serious" adverse event experienced by a patient participating in the Study and receiving Study Drug. For purposes of this requirement, "serious" means: (1) death; (2) in-patient hospitalization or prolonged hospitalization; (3) life-threatening; (4) persistent or significant disability or incapacity; (5) congenital anomaly or birth defect; or (6) other serious events that may jeopardize the patient and may require medical or surgical intervention to prevent one of the other five listed outcomes. Serious adverse events should be reported to Lilly using a CIOMS Form or other form acceptable to Lilly. Investigator and Institution further agree to make available promptly to Lilly such records as may be necessary and pertinent for Lilly to further investigate an adverse event in the Study that is possibly associated with the Study Drug.

SAE Reporting Email Address: mailindata_gsmtindy@lilly.com

7.6 Reporting Procedures to Genentech

Where the patient has been exposed to atezolizumab, serious adverse events (SAEs), AEs of Special Interest (AESIs), pregnancy reports, other Special Situation Reports, and Product Complaints with or without AE, as defined above (initial and follow-up), will be reported by the Coordinating Center to Genentech Drug Safety at usds_aereporting-d@gene.com or via fax (650-238-6067) twenty-four (24) hours of awareness, via the MedWatch Adverse Event Reporting form.

All Product Complaints without an AE should call via:
PC Hotline Number: (800) 334-0290 (M-F: 5 am to 5 pm PST)

Pregnancies will be followed up until the outcome of the pregnancy is known, whenever possible, based upon due diligence taken to obtain the follow-up information.

All written IND Safety Reports submitted to the FDA by the Investigator must also be faxed to Genentech Drug Safety:
Fax: (650) 225-4682 or (650) 225-4630
Email: usds_aereporting-d@gene.com
For questions related to safety reporting, please contact Genentech Drug Safety:
Tel: (888) 835-2555
Fax: (650) 225-4682 or (650) 225-4630

Reporting to Regulatory Authorities, Ethics Committees and Investigators

The Sponsor-Investigator will be responsible for the expedited reporting of safety reports originating from the Study to the Independent Ethics Committees/ Institutional Review Boards (IEC/IRB) of the Concerned Member States, where applicable.

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

And the Sponsor-Investigator will be responsible for the distribution of safety information to Site IRB: (617) 632-3029.

For questions related to safety reporting, please contact Genentech Drug Safety:
Tel: (888) 835-2555
Fax: (650) 225-4682 or (650) 225-4630

MedWatch 3500A Reporting Guidelines

In addition to completing appropriate patient demographic (Section A) and suspect medication information (Sections C & D), the report should include the following information within the Event Description (Section B.5) of the MedWatch 3500A form:

- Protocol number and title description

- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics (Section B.6)
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Follow-Up Information

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

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e., D.O.B., initials, patient number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

MedWatch 3500A (Mandatory Reporting) form is available at
https://www.fda.gov/media/69876/download

7.6.1 **Case Transmission Verification of Single Case Reports**

The Sponsor agrees to conduct the Case Transmission verification to ensure that all single case reports have been adequately received by Genentech via Investigator-Sponsor emailing Genentech a Quarterly line-listing documenting single case reports sent by Investigator-Sponsor 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 Investigator-Sponsor 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.

Reporting to Regulatory Authorities, Ethics Committees and Investigators

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.

Sponsor-investigator, as the Sponsor of the study, will be responsible for the expedited reporting of safety reports originating from the study to the European Medicine Agency (EMA) through Eudravigilance Clinical Trial Module (EVCTM), where applicable.

Sponsor-investigator will be responsible for the expedited reporting of safety reports originating from the study to the Independent Ethics Committees/ Institutional Review Boards (IEC/IRB) of the Concerned Member States, where applicable.

Sponsor-investigator, as the Sponsor of the study, will be responsible for the preparation of six-monthly Suspected Unexpected Serious Adverse Reaction (SUSAR) reports and their submission to Investigators, Regulatory Authorities and the Institutional Review Board/Independent Ethics Committee (IRB/IEC), where applicable

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

7.6.2 **Aggregate Reports**

Other Reports

Sponsor-Investigator will forward a copy of the Final Study Report to Genentech upon completion of the study.

7.7 Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports, sentinel events or unanticipated problems that require reporting per institutional policy.

7.8 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must <u>also</u> be reported in routine study data submissions.**

7.9 Study Close-Out

Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, 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

7.10 Queries

Queries related to the Study will be answered by Sponsor-Investigator. However, responses to all safety queries from regulatory authorities 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 atezolizumab. Sponsor-Investigator 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.

Both Parties will use all reasonable effort to ensure that deadlines for responses to urgent requests for information or review of data are met. The Parties will clearly indicate on the request the reason for urgency and the date by which a response is required.

7.11 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 the Sponsor of the Study, will be primarily responsible for assessment of the benefit-risk balance of the Study.
If **the Sponsor-Investigator** 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 **the Sponsor-Investigator** with signal and risk management activities related to the Product within the Study.

Genentech will also provide **the Sponsor-Investigator** with any new relevant information that may modify or supplement known data regarding the Product (e.g., relevant Dear Investigator Letter).

7.12 Compliance with Pharmacovigilance Agreement / Audit

The Parties shall follow their own procedures for adherence to AE reporting timelines.

Each Party 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 Agreement timelines. If there is any detection of trends of increasing or persistent non-compliance to transmission timelines stipulated in this Agreement, 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 Agreement, 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 Agreement 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. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agents administered in this study can be found in Section 7.1.

8.1 Abemaciclib

8.1.1 Mechanism of Action

Abemaciclib is an inhibitor of cyclin-dependent kinases 4 and 6 (CDK4 and CDK6). These kinases are activated upon binding to D-cyclins. In estrogen receptor-positive (ER+) breast cancer cell lines, cyclin D1 and CDK4/6 promote phosphorylation of the retinoblastoma protein (Rb), cell cycle progression, and cell proliferation. In vitro, continuous exposure to abemaciclib inhibited Rb phosphorylation and blocked progression from G1 into S phase of the cell cycle, resulting in senescence and apoptosis. In breast cancer xenograft models, abemaciclib dosed daily without interruption as a single agent or in combination with antiestrogens resulted in reduction of tumor size.

8.1.2 Pharmacokinetics

The pharmacokinetics of abemaciclib were characterized in patients with solid tumors, including metastatic breast cancer, and in healthy subjects. Following single and repeated twice daily dosing of 50 mg (0.3 times the approved recommended 150 mg dosage) to 200 mg of abemaciclib, the increase in plasma exposure (AUC) and Cmax was approximately dose proportional. Steady state was achieved within 5 days following repeated twice daily dosing, and the estimated geometric mean accumulation ratio was 2.3 (50% CV) and 3.2 (59% CV) based on Cmax and AUC, respectively. The absolute bioavailability of abemaciclib after a single oral dose of 200 mg is 45% (19% CV). The median Tmax of abemaciclib is 8.0 hours (range: 4.1-24.0 hours). A high-fat, high-calorie meal (approximately 800 to 1000 calories with 150 calories from protein, 250

calories from carbohydrate, and 500 to 600 calories from fat) administered to healthy subjects increased the AUC of abemaciclib plus its active metabolites by 9% and increased Cmax by 26%. In vitro, abemaciclib was bound to human plasma proteins, serum albumin, and alpha-1-acid glycoprotein in a concentration independent manner from 152 ng/mL to 5066 ng/mL. In a clinical study, the mean (standard deviation, SD) bound fraction was 96.3% (1.1) for abemaciclib, 93.4% (1.3) for M2, 96.8% (0.8) for M18, and 97.8% (0.6) for M20. The geometric mean systemic volume of distribution is approximately 690.3 L (49% CV). In patients with advanced cancer, including breast cancer, concentrations of abemaciclib and its active metabolites M2 and M20 in cerebrospinal fluid are comparable to unbound plasma concentrations. The geometric mean hepatic clearance (CL) of abemaciclib in patients was 26.0 L/h (51% CV), and the mean plasma elimination half-life for abemaciclib in patients was 18.3 hours (72% CV). Hepatic metabolism is the main route of clearance for abemaciclib. Abemaciclib is metabolized to several metabolites primarily by cytochrome P450 (CYP) 3A4, with formation of N-desethylabemaciclib (M2) representing the major metabolism pathway. Additional metabolites include hydroxyabemaciclib (M20), hydroxy-N-desethylabemaciclib (M18), and an oxidative metabolite (M1). M2, M18, and M20 are equipotent to abemaciclib and their AUCs accounted for 25%, 13%, and 26% of the total circulating analytes in plasma, respectively. After a single 150 mg oral dose of radiolabeled abemaciclib, approximately 81% of the dose was recovered in feces and approximately 3% recovered in urine. The majority of the dose eliminated in feces was metabolites.

8.1.3 Form

Abemaciclib, manufactured by Eli Lilly and Company, will be provided in the form of 50mg tablets in a bottle.

8.1.4 Administration

Doses should be taken at approximately the same times every day, spaced 12 hours apart, if there are at least 6 hours between doses, and with or without food. Tablets are to be swallowed whole and not chewed, crushed, or split. Vomited doses should be skipped, and abemaciclib dosing resumed at the next scheduled dose. If a dose is missed, it may be taken when remembered if there are at least 6 hours before the next scheduled dose. Broken, cracked, or otherwise not intact tablets should not be ingested. In the event a subject cannot be seen for a cycle visit due to COVID-19 infection or suspicion for COVID-19 infection, abemaciclib may be shipped upon approval of PI.

8.1.5 Storage and Stability

Storage conditions are described in the medication label.

8.1.6 Handling

Handling and disposal of abemaciclib should be per institutional guidelines for the handling and disposal of biologic and cytotoxic agents.

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

8.1.7 Availability

Abemaciclib will be provided for clinical trial use as 50mg tablets by Eli Lilly and Company.

8.1.8 Ordering

Eli Lilly and Company will supply abemaciclib and ordering will take place through Eli Lilly and Company. The study team will complete the Drug Request Form, which is kept as a separate document.

8.1.9 Accountability

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

8.1.10 Destruction and Return

Drug should be destroyed at the site, after the investigator approves the drug destruction policy at the site. Drug will not be returned to Eli Lilly and Company. Destruction will be documented in the Drug Accountability Record Form.

8.2 Atezolizumab

8.2.1 Mechanism of Action

Atezolizumab is a monoclonal antibody that binds to PD-L1 and blocks its interactions with both PD-1 and B7.1 receptors. This releases the PD-L1/PD-1 mediated inhibition of the immune response, including activation of the anti-tumor immune response without inducing antibody dependent cellular cytotoxicity. In syngeneic mouse tumor models, blocking PD-L1 activity resulted in decreased tumor growth.

8.2.2 Pharmacokinetics

Patients' exposure to atezolizumab increased dose proportionally over the dose range of 1 mg/kg to 20 mg/kg, including a dose of 1200 mg administered every 21 days. The clearance (CV%) was 0.20 L/day (29%), the volume of distribution at steady state was 6.9 L, and the terminal half-life was 27 days. Steady state is achieved after 6 to 9 weeks (2 to 3 cycles). The systemic accumulation ratio for area under the curve (AUC), maximum concentration (Cmax) and trough concentration (Cmin) was 1.9, 1.5 and 2.8-fold, respectively. Atezolizumab clearance was found to decrease over time, with a mean maximal reduction (CV%) from baseline value of approximately 17% (41%); however, the decrease in clearance was not considered clinically relevant.

8.2.3 Form

In the form of 1200 mg/20 mL (60 mg/mL) solution for injection in a single-dose vial will be provided by Genentech for the trial.

Atezolizumab injection is a sterile, preservative-free, and colorless to slightly yellow solution for intravenous infusion.

Visually inspect drug product for particulate matter and discoloration prior to administration, whenever solution and container permit. Discard the vial if the solution is cloudy, discolored, or visible particles are observed.

8.2.4 Administration

Prepare the solution for infusion as follows: Withdraw 20 mL of atezolizumab from the vial. Dilute into a 250 mL polyvinyl chloride (PVC), polyethylene (PE), or polyolefin (PO) infusion bag containing 0.9% Sodium Chloride Injection, USP. Dilute with 0.9% Sodium Chloride Injection only. Mix diluted solution by gentle inversion. Do not shake. Discard used or empty vials of atezolizumab. This product does not contain a preservative. Administer immediately once prepared. If diluted atezolizumab infusion solution is not used immediately, store solution either: at room temperature for no more than 6 hours from the time of preparation; this includes room temperature storage of the infusion in the infusion bag and time for administration of the infusion, or under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from time of preparation.

Administer through an intravenous line with or without a sterile, non-pyrogenic, low-protein binding in-line filter (pore size of 0.2–0.22 micron). Do not co-administer other drugs through the same intravenous line. Do not administer as an intravenous push or bolus.

8.2.5 Storage and Stability

Store vials under refrigeration at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze.

8.2.6 Handling

Handling and disposal of abemaciclib should be per institutional guidelines for the handling and disposal of biologic and cytotoxic agents.

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

8.2.7 Availability

Atezolizumab will be provided for clinical trial use by Genentech/Roche.

8.2.8 Ordering

Genentech/Roche will supply atezolizumab and ordering will take place through Genentech/Roche. The study team will complete the Drug Request Form, which is kept as separate document. All Drug Request Forms should be sent to the following email: anti-pdl- mpd3280a-gsur@gene.com

8.2.9 Accountability

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

8.2.10 Destruction and Return

Drug should be destroyed at the site, after the investigator approves the drug destruction policy at the site. Drug will not be returned to Genentech/Roche. Destruction will be documented in the Drug Accountability Record Form.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

The goal of the planned laboratory correlative studies is to correlate genetic and molecular features from tissue and blood specimens with therapeutic responses, and assess changes in immune microenvironment with abemaciclib with and without atezolizumab. Submission of samples for correlative studies is mandatory, unless patient safety is of concern.

9.1 Tissue Collection

Tissue will be collected at the time points specified in section 10. Please refer to the lab manual for additional sample collection and processing details.

9.1.1 Archival (pre-treatment) Specimen Requirements

Tissue from the most recent metastatic biopsy specimen is preferred, though tissue from primary prostate specimen is allowed if obtained after a patient developed metastatic disease. (Tissue from primary prostate tissue obtained prior to development of metastatic disease is not relevant to these studies.)

The ImmunoProfile assay utilizes 5-micron FFPE slides. Submit 5 unstained slides- if 5 slides are unavailable, submit at minimum either 3 unstained slides or 2 unstained slides with the adjacent H&E slide. ≥50% tumor tissue on each slide is preferred – thus if multiple biopsy specimens were obtained from a patient, the specimen to be sent should be prioritized by 1) metastatic (as opposed to primary) biopsy site 2) tumor content and 3) time interval prior to trial start (more recent specimens preferred).

9.1.2 On-Treatment Specimen Requirements

At least 4 (large bore) biopsy cores should be obtained as per institutional standards – 2 fresh frozen and at least 2 placed in formalin, for ImmunoProfiling and sequencing. The Investigator and interventional radiologist should decide on an appropriate biopsy site likely to yield tissue amenable to NGS analysis (80). Possible sites of biopsy are those felt to be of acceptable risk for research biopsy per institutional standards and may include lymph nodes, lung, bone, liver, and soft tissue. The window for the on-treatment biopsy can be extended per PI discretion if the patient required dose interruption(s) prior to the biopsy.

Specimen size requirements:

- Surface area of 25mm2 is optimal. Minimum of $5mm^2$.
- Volume of 1mm3 optimal. Minimum volume of $0.2mm^3$.

9.2 Blood Collection

Blood will be collected at the time points specified in section 10. Please refer to the lab manual for additional sample collection and processing details.

9.2.1 Archival (pre-treatment) Specimen Requirements

Two 10mL EDTA tubes will be collected to isolate buffy coat for germline DNA analysis. These tubes should be processed per the lab manual and stored at the registering institution until the patient is registered for the study. If the patient then does not enroll to the trial within 21 days, the respective buffy coats should be discarded. For patients who do enroll, the buffy coats will be shipped as per the lab manual.

9.2.2 On-Treatment Specimen Requirements

At each specified time point per section 10, Two x 10mL serum tubes, and 1 x 10mL Streck® tube will be collected for exome and cfDNA analysis.

9.3 Specimen Banking

Patient samples collected for this study will be retained at the institution where the assays above will be performed. Specimens will be stored indefinitely or until they are used up. If future use is denied or withdrawn by the patient, best efforts will be made to stop any additional studies and to destroy the specimens.

9.4 Analysis Plan for Correlative Studies

9.4.1 Immune infiltrate from tumor biopsies

An exploratory endpoint for this study is FoxP3+/CD8+ ratio paired differences between pre-treatment archival tissue and on-treatment biopsies. These paired differences will be compared between the unselected monotherapy group and the combination therapy group. We estimate that 15 patients will have evaluable pre-treatment and on-treatment biopsies per treatment group. In this case, the study will have at least 80% power to detect an effect size of 1.1 using a two-sided Mann-Whitney test at a 0.05 significance level. We are confident that both these effect size estimates are attainable and are clinically meaningful in this study population.

We will also explore correlation of immune infiltrate with genetic features as described below.

9.4.2 Genomic Biomarker

The prognostic value of genomic markers will be tested using the Cox proportional hazard regression model framework. The response variable will be PFS. Explanatory variables will include treatment arm and an indicator for presence of any somatic variant. The prognostic effect will be evaluated by the main effect test for the somatic variant indicator. To assess predictive value, the interaction between treatment arm and somatic variant will be tested. Similar tests will be performed for individual variants. Analysis on these correlative data is exploratory; no multiple comparison adjustment will be made.

9.4.3 Exosomal and tumoral whole-transcriptome sequencing

Exosomes are a type of extracellular vesicle that are secreted by all human cells (93). Tumor-derived exosomes are known to recapitulate the cellular RNA content. Because of their abundance in the peripheral blood in men with metastatic prostate cancer (94), exosome-based transcriptomics may provide an alternative to invasive needle-biopsies of metastatic tumor sites in this setting. We will explore the correlation of RNA-based biomarkers including AR splicing events (12)and signatures of AR signaling and cell cycle regulation, as well as “T cell inflamed” signature with clinical outcomes in each arm individually and in the combined cohort.

9.4.4 Circulating free DNA whole-genome sequencing

We will explore the correlation of genomic features (e.g., genetic alterations in the CDK4/6 pathway and in DNA repair pathways) with clinical outcomes in each arm individually and in the combined cohort. We will also correlate decrease in tumor fraction in cfDNA as (calculated from ultra-low pass whole genome sequencing using ichorCNA) from baseline to 6 weeks with PFS. In addition, we will identify new alterations at the time of progression to nominate mediators of resistance.

9.4.5 Whole exome sequencing from tumor biopsies

We will explore correlation of genetic features from on-treatment biopsy specimens (e.g., genetic alterations in the CDK4/6 pathway and in DNA repair pathways) with clinical outcomes in each arm individually and in the combined cohort. We will explore the correlation of loss-of-function alterations in genes involved with DNA damage repair, along with a variety of mutational signatures (mismatch repair deficiency, homologous recombination deficiency, tandem duplicator phenotype, mutational load, neoantigen burden) with composition of immune infiltrate as detected through ImmunoProfile. When genetic sequencing data from a prior tumor biopsy specimen is available, we will identify new genetic alterations to nominate mediators of cancer progression and resistance to prior therapies.

10. STUDY CALENDAR

Baseline evaluations are to be conducted within 21 days prior to registration. Scans and x-rays must be done $\leq$4 weeks prior to the start of therapy. Assessments must be performed prior to administration of any study agent. Study assessments and agents should be administered within $\pm$ 3 days of the protocol-specified date, unless otherwise noted.

Table 27. Study Calendar

Procedures	Screening[1]	Cycle 1 Day 1	Cycle 2 Day 1	Cycle 3 Day 1	Cycle 4+ Day 1	EOT[2]	Follow-Up[3]	EDC Timepoints
Informed Consent	X							NA
Physical Exam, Vital Signs, Weight[4]	X	X	X	X	X	X		Every cycle. Height only at screening
ECOG Performance Status	X	X	X	X	X	X		Screening, Every cycle, EOT
Toxicity Review[5]	X	X	X	X	X	X	X	Screening, Every cycle, EOT and Follow Up
Review of Concomitant Medications	X	X	X	X	X	X		Screening, Every cycle, EOT
CBC w/ Diff	X	X	X	X	X	X		Screening, Every cycle, EOT
Comprehensive Metabolic Panel	X	X	X	X	X	X		Screening, Every cycle, EOT
TSH, Free T4[6]		X	X[6]	X[6]	X	X		Cycle 1 day 1, Every cycle when collected, EOT
PSA	X	X	X	X	X	X	X	Screening, Every cycle, EOT and Follow up
Testosterone	X							Screening
Imaging & Response Assessment	X				X[7]		X	Screening, Every 3 cycles starting at C4D1, follow up
$Tc^{99}m$ Bone Scan	X				X[7]		X	Screening, Every 3 cycles starting at C4D1, follow up
PFTs	X[8]				X[8]			Screening and Cycle 4 Day 1
Research Blood	X[9]	X[9]		X[9]	X[9]	X[10]		C1D1, C3D1, C6D1, C9D1, C12D1, and EOT
Coagulation Blood Tests (PT/INR and aPTT)	X		X					
Archival Tumor Tissue	X[11]							Screening
On-treatment Tumor Biopsy				X[12]				**Cycle 3 D1**
Abemaciclib[13] (Dispensation, Diary Review & Reconciliation)		X	X	X	X	X		All cycles and EOT
Atezolizumab Administration[13]		X	X	X	X			All Cycles
Survival Status							X	Follow up

1. Baseline assessments must be completed within 21 days prior to registration.
2. Visit must be completed within 30 days of last dose of protocol therapy.
3. Survival follow-up every 3 months for 24 months post EOT visit ± 1 week. For subjects who discontinue treatment for reasons other than PD, scans should continue to be completed at regular intervals (approximately every 9 weeks or as per institutional standard), and PSA should continue to be measured at regular intervals (approximately every 3 weeks or as per institutional standard) until a new treatment is started, the patient withdraws from study procedures, or death.
4. Vital signs include temperature, pulse, respirations, blood pressure. Height will be obtained at screening only. Physical exam can be excluded when a virtual visit is required due to COVID-19 pandemic.
5. Data on adverse events will be collected from the time of the initial study drug administration through 100 days after the last dose of study drug, Data will also be collected regarding any serious adverse event that occurs more than 100 days after the last dose of study drug(s) and is considered related to study drug.
6. Only required for patients receiving atezolizumab-containing regimens on cycle 1 day 1 and every 3 cycles, otherwise only as clinically indicated.
7. MRI or CT of abdomen and pelvis along with chest CT with or without IV contrast. Brain CT or MRI with (preferred) or without IV contrast as indicated. To be assessed every 3 cycles (-1 week window) beginning with C4D1, i.e. within 1 week of planned C4D1, C7D1, etc. If the initiation of cycle 4, cycle 7, etc. is planned to be delayed (for toxicity management, scheduling, or any other reason), then imaging should be delayed as well. However, if imaging studies are performed and intercurrent toxicities preclude initiation of C4D1, C7D1, etc. within 1 week, the imaging does not need to be repeated prior to eventual initiation of the next treatment cycle.
8. PFTs include spirometry, lung volumes and DLCO. If PFTs after 3 months of trial therapy do not meet criteria for grade 1 or higher pneumonitis/ILD, then further monitoring PFTs are not required. If a patient develops grade 1 or higher pneumonitis/ILD, PFTs should be obtained every 8 weeks until resolution; if a patient develops grade 2 or higher pneumonitis/ILD, they must be discontinued from trial therapy.
9. Research blood at time of screening is whole blood collected in EDTA tube to isolate buffy coat for germline DNA, at subsequent time points are 2 × 10mL serum tubes for exosome analysis, and 1 × 10mL Streck® tube for cfDNA analysis. Collect C1D1 prior to administration of protocol therapy and after completing 2 cycles of protocol therapy ± 14 days. Collection also at C6D1, C9D1, and C12D1 ± 3 business days.
10. May be collected and submitted up to 30 days after progression and prior to any intervening treatment. If progression collection is within 14 days of prior correlative blood collection, these research samples do not need to be collected.
11. Refer to section 9.1 for specimen requirement details.
12. Required after completing 2 cycles of protocol therapy ± 7 days, for all patients. Refer to section 9.1 for specimen requirement details.
13. Based on regimen randomized and/or enrolled to, as per section 5.

NOTE: All assessments have a window of ± 3 business days unless otherwise mentioned. Additional flexibility (within reason) may be permitted in cases such as vacation and inclement weather; this is at the discretion of the Sponsor-Investigative team (whenever possible, team should be notified in advance), and such situations must be clearly documented.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect

For the purposes of this study, participants should be re-evaluated for response every 3 cycles (+/- 7 days). In addition to a baseline scan, confirmatory scans should also be obtained not less than 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using Prostate Cancer Working Group 3 (PCWG3) modifications (81) (section 11.2) to the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the modified RECIST criteria. Response and progression of osseous disease by bone scintigraphy will be per PCWG3 criteria (81).

11.1.1 Definitions

Evaluable for Target Disease response. Only those participants who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for target disease response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Participants who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10mm by CT scan (irrespective of scanner type) for studies with a slice thickness of ≤5mm or twice the slice thickness or MRI
- 10mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be record as non-measurable)
- 20mm by chest X-ray (if clearly defined and surrounded by aerated lung)

All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a

lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Note: Tumor lesions that are situated in a previously irradiated area will only be considered measurable if they have had subsequent progression by at least 5mm.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter < <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions without measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

Target lesions. All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organ(s), but in addition should be those that lend themselves to reproducible repeated measurements. If a non-nodal lesion is either not present or is initially measured with longest diameter <10mm as a non-target then grows to >10mm after baseline, this lesion is assessed as a new target lesion as per iRECIST criteria (80). Per iRECIST, new lesions are assessed as per RECIST 1.1 but are recorded separately on the case report form (but not included in the sum of lesions for target lesions identified at baseline).

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 15 mm x 30mm has a short axis of 15 mm and qualifies as a malignant, measurable node. In this example, 15 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease. If a non-target

lymph node grows to >15 mm after baseline, this node is assessed as a new target lesion as per iRECIST. Per iRECIST, new lesions are assessed as per RECIST 1.1 but are recorded separately on the case report form (but not included in the sum of lesions for target lesions identified at baseline).

Non-target lesions. All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g., 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

11.1.3 Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation using a ruler, calipers, or a digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm in diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung; however, CT is preferable.

Conventional CT and MRI. This guideline has defined measurability of lesions on CT scan based on the assumption that CT thickness is 5mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size of a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be

measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later data and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure from CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy. The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

PSA response and progression.
PSA response is defined per section 11.1.7, and PSA progression is defined per section 11.1.8.

Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

11.1.4 Response Criteria

11.1.4.1 Evaluation of Target Lesions

Prior to the first PD assessment, patients will be evaluated according to the following RECISTv1.1 response:

Complete Response (CR): Disappearance of all target lesions, determined by two separate observations conducted not less than 4 weeks apart. There can be no appearance of new* lesions.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters. There can be no appearance

of new* lesions.

Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions (with a minimum absolute increase of 5 mm), taking as reference the smallest sum LD recorded since the treatment started, or the appearance of one or more new* lesions.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR (taking as reference the baseline sum LD) nor sufficient increase to qualify for PD (taking as reference the smallest sum LD since the treatment started).

For patients receiving atezolizumab only:
After the first PD assessment per RECISTv1.1 (=iUPD per iRECIST), patients will be evaluated for iCPD 4-8 weeks later according to the following definition:

Immune Unconfirmed Progressive Disease (iUPD): At least a 20% increase in the sum of the LD of target lesions (with a minimum absolute increase of 5 mm), taking as reference the smallest sum LD recorded since the treatment started, or appearance of new* lesions since the last evaluation.

Immune Confirmed Progressive Disease (iCPD): If iUPD was assigned based on increase in size of target or non-target lesions, iCPD is assigned if a further increase in size of lesions is observed or if new lesions appear. If iUPD was assigned based only on the development of new lesions, iCPD is only assigned if at next assessment additional new lesions appear or an increase in size of new lesions is seen (≥5 mm for sum of new lesion target or any increase in new lesion non-target).

*excludes skeletal lesions

11.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes should be non-pathological in size (<10 mm short axis).

Incomplete Response/Stable Disease (SD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

Although a clear progression on non-target lesions in absence of stable target lesions is exceptional, the opinion of the treating physician should prevail in such circumstances.

11.1.4.3 Evaluation of New Lesions

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

11.1.4.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Evaluation as per RECISTv1.1 and iRECIST

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response per RECIST 1.1**	**Overall Response per iRECIST *(Cohort B and C)***	**Best Response for this Category Also Requires:**
CR	CR	No	CR	iCR	≥4 wks. confirmation
CR	CR Non-CR/SD	No	PR	iPR	≥4 wks. confirmation
PR	CR Non-CR/PD	No			
SD	CR Non-CR/PD	No	SD	iSD	documented at least once ≥4 wks. from baseline
PD	Any	Any	PD	iUPD	4-8 wks. from baseline for iUPD per iRECIST
Any	PD*	Any			
Any	Any	Yes			
PD	Any	Any	NA	iCPD	No further confirmation required
Any	PD*	Any			
Any	Any	Yes			

*In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
NA – Not applicable

Note:	Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

11.1.5 Safety/Tolerability

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the CTCAE version 5.0 for reporting of adverse events (http://ctep.cancer.gov/reporting/ctc.html).

11.1.6 6-month progression free survival (PFS) rate

PFS is defined as the duration of time from the start of treatment to disease progression (as defined by PCWG3 criteria (79) for Arm A and modified by iRECIST criteria (80) for Arms B and C), or death, whichever occurs first. In brief, progression by PCWG3 criteria is clinical progression, soft tissue progression by RECIST v1.1, or bone scan progression (the development of 2 new lesions compared to the 1st post-treatment bone scan as baseline). These criteria apply to patients with both measurable and non-measurable disease at baseline. PSA progression alone does not meet criteria for progression according to PCWG3 criteria.

Radiographic disease progression is modified by immune-related criteria for patients in Arms B and C. Patients in Arms B and C for whom first restaging studies demonstrate PD per RECISTv1.1 (=iUPD per iRECIST) but who are treated beyond progression per section 5.8 are not considered to have disease progression unless the subsequent confirmatory scan demonstrates Immune Confirmed Progressive Disease (iCPD) per section 11.1.4.1. If the confirmatory scan demonstrates iCPD, then the date of progression is the date of original PD by RECIST 1.1; otherwise the date of progression is date of iCPD.

11.1.7 Objective Response Rate (ORR)

ORR will be defined as the proportion of subjects who experience radiographic response (complete response or partial response) by RECIST 1.1 criteria OR PSA response.

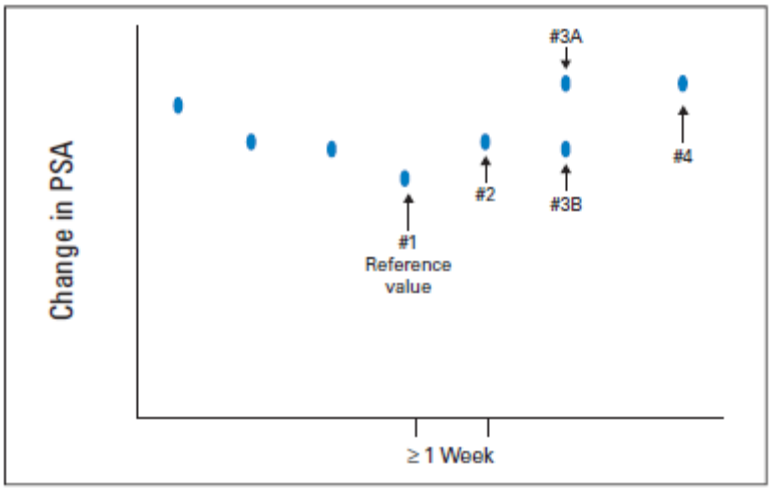
Per PCWG3 criteria, PSA response is defined by at least 50% decline in PSA level from baseline measured twice at least 3 weeks apart. Based on PCWG3 criteria, a favorable effect on PSA may be delayed for ≥ 12 weeks. PSA will be monitored every 3 weeks, but early rises in PSA before 12 weeks will not be considered when determining PSA response, i.e. PSA response will be determined in relation to baseline even if PSA initially rises after starting on trial therapy.

11.1.8 Criteria for PSA Progression

For rising PSA after an initial decline from baseline, the PSA is recorded from the start of therapy to first PSA increase that is ≥ 25% and ≥ 2ng/mL above the nadir, which is confirmed by a second value 4 or more weeks later, confirming a rising trend. If there is no initial decline from

baseline, PSA progression is defined as ≥ 25% increase and ≥ 2 ng/mL increase from baseline **beyond 12 weeks**.

Patients who have only documented PSA progression in the absence of radiographic or clinical progression should continue on study therapy.



11.1.9 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for PSA or radiographic response until the first date that PCWG3 progression is documented, or if there is interval development of recurrent or progressive disease based on clinical, soft tissue or bone scan progression by PCWG3 criteria.

11.2 Radiographic Disease Criteria

All radiographic response criteria are as per PCWG3 criteria summarized below.

11.2.1 Nodal Disease

Up to five (5) lesions are recorded per site of disease. These will be assessed as per RECIST 1.1 with the following PCWG3 caveats:

1. Changes in size are recorded using a waterfall plot
2. Favorable change is confirmed with a second scan
3. Complete elimination of disease at any site is recorded separately
4. Only changes in lymph nodes that were ≥15 mm in the short axis are reported
5. Changes in pelvic (regional) nodes versus extrapelvic (distant/metastatic) nodes are recorded separately

11.2.2 Visceral Disease

Visceral disease includes lesions in lung, liver, adrenal, and CNS sites. These will be assessed as per RECIST 1.1 with the following PCWG3 caveats:

1. Changes in liver, lung, adrenal, and CNS sites are recorded separately
2. Only changes in lesions ≥1.0 cm in the longest dimension are reported

11.2.3 Bone Disease

Bone disease is evaluated as per PCWG3 criteria, with changes recorded as improved or stable (no new lesions) or worse (new lesions). Additional PCWG3 caveats include:

1. Changes in intensity of uptake alone do not constitute progression or regression
2. No new lesions: continue therapy in absence of other signs of progression
3. New lesions (progression) is defined by the following per PCWG3:
    a. Exclude pseudoprogression in the absence of symptoms or other signs of progression
    b. At least two new lesions on first post-treatment scan, with at least two additional lesions on the next scan (2+2 rule)
    c. If at least two additional new lesions are seen on the next (confirmatory) scan, the date of progression is the date of the first post-treatment scan, when the first two new lesions were documented
    d. For scans after the first post-treatment scan, at least two new lesions relative to the first post-treatment scan confirmed on a subsequent scan

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 Method

The DF/HCC Office of Data Quality (ODQ) will collect, manage, and perform quality checks on the data for this study.

12.1.2 Responsibility for Data Submission

Investigative sites are responsible for submitting data and/or data forms to the Office of Data Quality (ODQ) in accordance with DF/HCC policies.

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Board (DSMB) will review and monitor study progress, toxicity, safety and other data from this study. The Board is chaired by a medical oncologist from outside of DF/HCC and its membership composed of internal and external institutional representation. Information that raises any questions about participant safety or

protocol performance will be addressed by the Sponsor-Investigator, statistician and study team. Should any major concerns arise, the DSMB will offer recommendations regarding whether or not to suspend the study.

The DSMB will meet twice a year to review accrual, toxicity, response and reporting information. Information to be provided to the DSMB may include: participant accrual; treatment regimen information; all adverse events and serious adverse events reported across all sites by category; summary of any deaths on study; audit results; and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 Multi-Center Guidelines

This protocol will adhere to DF/HCC Policy MULTI-100 and the requirements of the DF/HCC Multi-Center Data and Safety Monitoring Plan. The specific responsibilities of the Sponsor-Investigator, Coordinating Center, and Participating Institutions and the procedures for auditing are presented in Appendix B.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

13.1.1 Primary Endpoints

- Co-primary endpoints for efficacy are 6-month progression free survival (PFS) rate and objective response rate (ORR).
    - PFS is defined as the duration of time from the start of treatment to disease progression (as defined by PCWG3 criteria), or death, whichever occurs first (for detailed definition please see Section 11.1.6).
    - ORR is the proportion of evaluable patients who had radiographic response (complete response or partial response) by RECIST 1.1 criteria OR 50% decline in PSA from pretreatment baseline per PCWG3 criteria (for detailed definition please see Section 11.1.7).
- Primary endpoint for dose safety for abemaciclib cohort Arm C (for detailed definition please see Section 7.3).

13.1.2 Secondary Endpoint

- Clinical benefit rate (CBR) estimated by proportion of evaluable patients who had complete response (CR), partial response (PR) or stable disease (SD) as their best response to treatment by PCWG3 criteria in Arm A.
- Duration of response (DOR), duration of therapy (DOT), and time to progression (TTP) among responders by PCWG3 criteria in Arm A.
- Overall survival (OS) in Arms A..
- Safety endpoints include the number and severity of adverse events by CTCAE 5.0 in all

Arms.

13.1.3 Exploratory/Translational Endpoint

- Efficacy (6-month PFS, ORR, CBR, ORR, DOR, DOT, TTP, OS) of atezolizumab alone and abemaciclib alone in the CDK12 loss cohort (Arm C).
- From mandatory on-treatment tissue biopsies:
    1. Assessment of FoxP3+/CD8+ ratio in each treatment arm by multiplex immunofluorescence (primary biomarker endpoint).
    2. Assessment of FoxP3+/CD8+ ratio in on-treatment tumor biopsies compared to archival tissue specimens by multiplex immunofluorescence in each treatment arm.
    3. Correlation of AR aberrations (specifically, AR variants and AR amplifications) detected by targeted exome-sequencing or whole transcriptome sequencing with response and resistance to therapy.
    4. Correlation of genomic features (including alterations in CDK4/6 and DNA damage repair pathways, mutational load, neoantigen burden) detected by targeted exome sequencing with response and resistance to therapy.
    5. Assessment of markers of AR pathway activation, pharmacodynamic markers of CDK4/6 inhibition as well as DNMT1 and genes involved with antigen presentation and interferon signaling through whole transcriptome sequencing.
- From plasma collected pre-treatment, on-treatment (6 weeks after starting therapy), and at progression ("Liquid-biopsies"):
    1. Correlation of AR aberrations (specifically, AR variants and AR amplifications) between circulating blood exosomes and tumor tissue.
    2. Correlation of genomic features (including alterations in CDK4/6 and DNA damage repair pathways, mutational load, neoantigen burden) between circulating blood exosomes and tumor tissue.

13.2 Primary Efficacy Endpoint Statistical Plan and Sample Size

A two-stage design with dichotomous co-primary endpoints 6-month progression-free survival (6m-PFS) and objective response rate (ORR; PSA reduction by greater than 50% or radiographic response by RECIST 1.1) will be used to accrue approximately 27 patients in arm A (95). This study achieves 86% power for 6-month progression-free survival (with null 6m-PFS 12% (7) and alternative of 34%) and 85% power for response (with null ORR 10% (38) and alternative of 30%) simultaneously at a one-sided alpha 0.08. The study will accrue 12 patients at the first stage of arm A and will be terminated with 37% of probability of early stopping if no patient responds and no patient is progression-free at 6 months. The number of patients with 6m-PFS and objective response are independent to each other. Stage 2 will accrue 15 additional patients, leaving a cumulative accrual of 27 patients in arm A. If 6 patients experience 6m-PFS or 5 patients have an objective response by the end of stage 2, this study would suggest meaningful clinical activity.

We assume an accrual rate of 4 patients per month (2 per arm) for all sites combined. Accrual

duration of stage 1 will be 6 months and the enrollment will be paused maximum 6 months after enrolling 12th patient to observe the patient's response. If arm A opens stage 2 then another 8 months will be expected for accrual.

For arm C (CDK12 loss CRPC), similar assumptions will be made with expected efficacy with a null 6m-PFS rate of 12% and an alternative rate of 34% or greater. Due to accrual limitations in this arm, we will use a single stage design. Five patients with CDK12 loss will be accrued to an atezolizumab monotherapy as an exploratory group. Then, additional subjects with CDK12 loss will be accrued to therapy with abemaciclib.
A one-sided, one-sample log-rank test calculated from a sample of 16 subjects treated with abemaciclib alone achieves 80-85% power at a 0.05 significance level to detect a 6m-PFS proportion of 34% in this population with the combined treatments when the 6m-PFS in the historic control group is 12%. Accrual duration will be 18 months, the same period of accrual as arm A. Follow-up continues for 12 months after the last subject is accrued. The expected number of events during the study is 14-16. It is assumed that the PFS time distributions of both groups are approximated reasonably well by the exponential distribution.

For the patients treated with abemaciclib alone in each arm A and C, the 6m-PFS and 90% confidence interval will be estimated using Kaplan-Meier method and ORR with 90% binomial confidence interval will be summarized. The efficacy endpoints of 6m-PFS and ORR in patients treated with combination of abemaciclib and atezolizumab in arm B will be listed individually due to small number.

13.3 Primary Safety Endpoint Statistical Plan

Safety and tolerability for abemaciclib monotherapy and for the combination of abemaciclib and atezolizumab will be summarized by rate of dose-limiting toxicities (DLTs) as defined in section 7.3 using percentage and 90% confidence interval, and by incidence and grade of adverse events (AEs) by CTCAE version 5.0. Safety analyses will be performed for all patients who have received at least one dose of study drug.

Bayesian toxicity monitoring (https://trialdesign.org/one-page-shell.html#BTOX) was planned to be used for all patients enrolled to Arm B and to the combination treatment cohort of Arm C (up to a maximum of 43 patients) starting after three patients have initiated treatment. If the rate of patients experiencing dose limiting toxicities (DLTs) at the starting dose exceeded the pre-specified threshold for excessive toxicity, then subsequent patients randomized to Arm B or enrolled to the combination cohort of Arm C were planned to de-escalate abemaciclib dose to 100 mg BID with atezolizumab 1200 mg every 21 days with Bayesian toxicity monitoring resuming once three additional patients have initiated treatment at this lower dose level. If the rate of patients experiencing DLT at the de-escalated dose exceeded the pre-specified threshold for excessive toxicity, then enrollment to Arm B and the combination cohort of Arm C were planned to be halted. Maximum probability of DLT is 0.3 with prior distribution of B(0.5, 0.5) for the DLT rate. Stopping probability threshold for excessive DLT is 0.7. Dose de-escalation or early stopping of enrollment for combination cohort will follow the rules displayed in Table 28.

Table 28. Decision rules for dose de-escalation or early stopping

# DLT-evaluable[1] patients treated at current dose level	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	
Reduce dose or stop early if # pts experiencing DLT is >	2	2	2	3	3	4	4	4	5	5	5	6	6	6	7	7	7	8	8	8	
# DLT-evaluable[1] patients treated at current dose level	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43
Reduce dose or stop early if # of pts experiencing DLT is >	9	9	9	9	10	10	10	11	11	11	12	12	12	13	13	13	14	14	14	15	15

[1]Patients must have received at least 28 days of trial therapy (or have experienced a DLT) to be considered DLT-evaluable.

Table 29. Operating characteristics under 5 scenarios of true DLT rates

Scenario	Probability of true DLT	Probability of dose de-escalation or early stopping	Probability of declaring DLT	Average # patients	Average # pts w/ DLTs	Observed DLT rate
1	0.1	0.09	0.09	39.6	4.0	0.13
2	0.2	0.34	0.34	30.6	6.1	0.29
3	0.3	0.71	0.71	18.7	5.6	0.43
4	0.4	0.94	0.95	9.6	3.9	0.52
5	0.5	1.00	1.00	5.6	2.8	0.59

Due to two grade 5 sepsis events observed in the 8 patients treated on Arm B with unclear relationship to the study medications, the Sponsor-Investigator and co-investigators elected to halt enrollment to combination treatment rather than following the Bayesian toxicity monitoring plan. Unselected patients will continue to enroll on Arm A in a non-randomized fashion (up to 27 patients in total in Arm A) and patients with CDK12 loss subsequently enrolled on Arm C after the 5 patients treated with atezolizumab monotherapy will receive abemaciclib 200 mg BID as monotherapy (total enrollment on Arm C up to 21 patients in total).

13.4 Secondary Endpoint Analysis Plan

Clinical benefit rate estimated by proportion of evaluable patients who had complete response (CR), partial response (PR) or stable disease (SD) as their best response to treatment will be reported by treatment arm with 95% binomial confidence intervals. Overall survival (OS) among all patients, and among responders, duration of response (DOR), duration of therapy (DOT), and time to progression (TTP) will each be reported by treatment arm using Kaplan-Meier methods. Safety endpoints including the number and severity of adverse events will be summarized for each treatment arm using counts and proportions.

13.5 Statistical Plan for Primary Exploratory Endpoint Requiring Biopsies

The primary biomarker study from the mandatory on-treatment biopsy for unselected mCRPC will be FoxP3+/CD8+ T-cell ratio. We expect the ratio of FoxP3+/CD8+ T-cells in archival pre-treatment tissue to be ~10% (96). We expect this ratio to decrease to ~5% with abemaciclib monotherapy. With 27 patients in arm A, we expect 22 samples in each arm to be evaluable for this endpoint. The FoxP3+/CD8+_T-cell ratio in all biopsy specimens and the change between pre-treatment and on-treatment specimens will be reported descriptively in each treatment arm separately. The study will have at least 80% power at a 0.05 significance level to detect an effect size of 0.90 in change in FoxP3+/CD8+ T-cells ratio means between the combination group and the monotherapy group, using a two-sided Mann-Whitney test.

14. PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

REFERENCES

1. Siegel RL, Miller KD, and Jemal A. Cancer statistics, 2020. *CA Cancer J Clin.* 2020;70(1):7-30.
2. de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, et al. Abiraterone and increased survival in metastatic prostate cancer. *The New England journal of medicine.* 2011;364(21):1995-2005.
3. Ryan CJ, Smith MR, Fizazi K, Saad F, Mulders PF, Sternberg CN, et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol.* 2015;16(2):152-60.
4. Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *The New England journal of medicine.* 2012;367(13):1187-97.
5. Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. *The New England journal of medicine.* 2014;371(5):424-33.
6. Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *The New England journal of medicine.* 2004;351(15):1502-12.
7. de Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels JP, Kocak I, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet.* 2010;376(9747):1147-54.
8. Kantoff PW, Higano CS, Shore ND, Berger ER, Small EJ, Penson DF, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *The New England journal of medicine.* 2010;363(5):411-22.
9. Parker C, Nilsson S, Heinrich D, Helle SI, O'Sullivan JM, Fossa SD, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *The New England journal of medicine.* 2013;369(3):213-23.
10. Sartor O, de Bono J, Chi KN, Fizazi K, Herrmann K, Rahbar K, et al. Lutetium-177-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer. *The New England journal of medicine.* 2021;385(12):1091-103.
11. Hussain M, Mateo J, Fizazi K, Saad F, Shore N, Sandhu S, et al. Survival with Olaparib in Metastatic Castration-Resistant Prostate Cancer. *The New England journal of medicine.* 2020;383(24):2345-57.
12. Cancer Genome Atlas Research N. The Molecular Taxonomy of Primary Prostate Cancer. *Cell.* 2015;163(4):1011-25.
13. Robinson D, Van Allen EM, Wu YM, Schultz N, Lonigro RJ, Mosquera JM, et al. Integrative clinical genomics of advanced prostate cancer. *Cell.* 2015;161(5):1215-28.
14. Henzler C, Li Y, Yang R, McBride T, Ho Y, Sprenger C, et al. Truncation and constitutive activation of the androgen receptor by diverse genomic rearrangements in prostate cancer. *Nature communications.* 2016;7:13668.

15. Sharp A, Coleman I, Yuan W, Sprenger C, Dolling D, Rodrigues DN, et al. Androgen receptor splice variant-7 expression emerges with castration resistance in prostate cancer. *J Clin Invest.* 2019;129(1):192-208.
16. Armenia J, Wankowicz SAM, Liu D, Gao J, Kundra R, Reznik E, et al. The long tail of oncogenic drivers in prostate cancer. *Nat Genet.* 2018.
17. Abida W, Armenia J, Gopalan A, Brennan R, Walsh M, Barron D, et al. Prospective Genomic Profiling of Prostate Cancer Across Disease States Reveals Germline and Somatic Alterations That May Affect Clinical Decision Making. *JCO Precis Oncol.* 2017;2017.
18. Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, et al. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. *The New England journal of medicine.* 2015;372(26):2509-20.
19. de Bono J, Mateo J, Fizazi K, Saad F, Shore N, Sandhu S, et al. Olaparib for Metastatic Castration-Resistant Prostate Cancer. *The New England journal of medicine.* 2020;382(22):2091-102.
20. Abida W, Campbell D, Patnaik A, Sautois B, Shapiro J, Vogelzang NJ, et al. Preliminary results from the TRITON2 study of rucaparib in patients with DNA damage repair (DDR)-deficient metastatic castration-resistant prostate cancer (mCRPC): updated analyses. *METHODS.* 2019.
21. Abida W, Cheng ML, Armenia J, Middha S, Autio KA, Rathkopf DE, et al.: American Society of Clinical Oncology; 2018.
22. Antonarakis ES, Shaukat F, Isaacsson Velho P, Kaur H, Shenderov E, Pardoll DM, et al. Clinical Features and Therapeutic Outcomes in Men with Advanced Prostate Cancer and DNA Mismatch Repair Gene Mutations. *European urology.* 2018.
23. Han GC, Hwang J, Wankowicz SAM, Zhang Z, Liu D, Cibulskis C, et al. Genomic Resistance Patterns to Second-Generation Androgen Blockade in Paired Tumor Biopsies of Metastatic Castration-Resistant Prostate Cancer. *JCO Precision Oncology.* 2017(1):1-11.
24. Korpal M, Korn JM, Gao X, Rakiec DP, Ruddy DA, Doshi S, et al. An F876L mutation in androgen receptor confers genetic and phenotypic resistance to MDV3100 (enzalutamide). *Cancer Discov.* 2013;3(9):1030-43.
25. Stice JP, Wardell SE, Norris JD, Yllanes AP, Alley HM, Haney VO, et al. CDK4/6 Therapeutic Intervention and Viable Alternative to Taxanes in CRPC. *Mol Cancer Res.* 2017;15(6):660-9.
26. Goel S, DeCristo MJ, Watt AC, BrinJones H, Sceneay J, Li BB, et al. CDK4/6 inhibition triggers anti-tumour immunity. *Nature.* 2017;548(7668):471-5.
27. Zhang J, Bu X, Wang H, Zhu Y, Geng Y, Nihira NT, et al. Cyclin D-CDK4 kinase destabilizes PD-L1 via cullin 3-SPOP to control cancer immune surveillance. *Nature.* 2018;553(7686):91-5.
28. Jerby-Arnon L, Shah P, Cuoco MS, Rodman C, Su MJ, Melms JC, et al. A Cancer Cell Program Promotes T Cell Exclusion and Resistance to Checkpoint Blockade. *Cell.* 2018;175(4):984-97 e24.
29. Schaer DA, Beckmann RP, Dempsey JA, Huber L, Forest A, Amaladas N, et al. The CDK4/6 Inhibitor Abemaciclib Induces a T Cell Inflamed Tumor Microenvironment and

Enhances the Efficacy of PD-L1 Checkpoint Blockade. *Cell reports.* 2018;22(11):2978-94.
30. Sherr CJ, Beach D, and Shapiro GI. Targeting CDK4 and CDK6: From Discovery to Therapy. *Cancer Discov.* 2016;6(4):353-67.
31. Gelbert LM, Cai S, Lin X, Sanchez-Martinez C, Del Prado M, Lallena MJ, et al. Preclinical characterization of the CDK4/6 inhibitor LY2835219: in-vivo cell cycle-dependent/independent anti-tumor activities alone/in combination with gemcitabine. *Invest New Drugs.* 2014;32(5):825-37.
32. Tate SC, Cai S, Ajamie RT, Burke T, Beckmann RP, Chan EM, et al. Semi-mechanistic pharmacokinetic/pharmacodynamic modeling of the antitumor activity of LY2835219, a new cyclin-dependent kinase 4/6 inhibitor, in mice bearing human tumor xenografts. *Clinical cancer research : an official journal of the American Association for Cancer Research.* 2014;20(14):3763-74.
33. O'Leary B, Finn RS, and Turner NC. Treating cancer with selective CDK4/6 inhibitors. *Nat Rev Clin Oncol.* 2016;13(7):417-30.
34. Finn RS, Martin M, Rugo HS, Jones S, Im SA, Gelmon K, et al. Palbociclib and Letrozole in Advanced Breast Cancer. *The New England journal of medicine.* 2016;375(20):1925-36.
35. Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, Paluch-Shimon S, et al. Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer. *The New England journal of medicine.* 2016;375(18):1738-48.
36. Goetz MP, Toi M, Campone M, Sohn J, Paluch-Shimon S, Huober J, et al. MONARCH 3: Abemaciclib As Initial Therapy for Advanced Breast Cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2017;35(32):3638-46.
37. Dickler MN, Tolaney SM, Rugo HS, Cortes J, Dieras V, Patt D, et al. MONARCH 1, A Phase II Study of Abemaciclib, a CDK4 and CDK6 Inhibitor, as a Single Agent, in Patients with Refractory HR(+)/HER2(-) Metastatic Breast Cancer. *Clinical cancer research : an official journal of the American Association for Cancer Research.* 2017;23(17):5218-24.
38. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *The New England journal of medicine.* 2012;366(26):2443-54.
39. Hansen AR, Massard C, Ott PA, Haas NB, Lopez JS, Ejadi S, et al. Pembrolizumab for advanced prostate adenocarcinoma: findings of the KEYNOTE-028 study. *Annals of oncology : official journal of the European Society for Medical Oncology.* 2018;29(8):1807-13.
40. De Bono JS, Goh JC, Ojamaa K, Piulats Rodriguez JM, Drake CG, Hoimes CJ, et al.: American Society of Clinical Oncology; 2018.
41. Lawrence MS, Stojanov P, Polak P, Kryukov GV, Cibulskis K, Sivachenko A, et al. Mutational heterogeneity in cancer and the search for new cancer-associated genes. *Nature.* 2013;499(7457):214-8.
42. Gevensleben H, Dietrich D, Golletz C, Steiner S, Jung M, Thiesler T, et al. The Immune Checkpoint Regulator PD-L1 Is Highly Expressed in Aggressive Primary Prostate

Cancer. *Clinical cancer research : an official journal of the American Association for Cancer Research.* 2016;22(8):1969-77.
43. Rooney MS, Shukla SA, Wu CJ, Getz G, and Hacohen N. Molecular and genetic properties of tumors associated with local immune cytolytic activity. *Cell.* 2015;160(1-2):48-61.
44. Bishop JL, Sio A, Angeles A, Roberts ME, Azad AA, Chi KN, et al. PD-L1 is highly expressed in Enzalutamide resistant prostate cancer. *Oncotarget.* 2015;6(1):234-42.
45. Graff JN, Beer TM, Alumkal JJ, Slottke RE, Redmond WL, Thomas GV, et al. A phase II single-arm study of pembrolizumab with enzalutamide in men with metastatic castration-resistant prostate cancer progressing on enzalutamide alone. *J Immunother Cancer.* 2020;8(2).
46. Graff JN, Antonarakis ES, Hoimes CJ, Tagawa ST, Hwang C, Kilari D, et al.: American Society of Clinical Oncology; 2020.
47. Conter HJ, Shore ND, Berry WR, Fong PC, Piulats Rodriguez JMM, Appleman LJ, et al.: American Society of Clinical Oncology; 2020.
48. Powles T, Yuen KC, Gillessen S, Kadel EE, 3rd, Rathkopf D, Matsubara N, et al. Atezolizumab with enzalutamide versus enzalutamide alone in metastatic castration-resistant prostate cancer: a randomized phase 3 trial. *Nature medicine.* 2022.
49. Morris MJ, Fong L, Petrylak DP, Sartor AO, Higano CS, Pagliaro LC, et al.: American Society of Clinical Oncology; 2020.
50. Agarwal N, Loriot Y, McGregor BA, Dreicer R, Dorff TB, Maughan BL, et al.: American Society of Clinical Oncology; 2020.
51. Pujol J-L, Vansteenkiste JF, Paz-Ares LG, Gregorc V, Mazieres J, Awad MM, et al.: American Society of Clinical Oncology; 2020.
52. Rugo HS, Kabos P, Beck JT, Chisamore MJ, Hossain A, Chen Y, et al.: American Society of Clinical Oncology; 2020.
53. Rugo HS, Beck JT, Jerusalem G, Wildiers H, Kabos P, Chisamore M, et al. *AACR Annual Meeting 2020*.
54. Wang Y, Zhou S, Yang F, Qi X, Wang X, Guan X, et al. Treatment-Related Adverse Events of PD-1 and PD-L1 Inhibitors in Clinical Trials: A Systematic Review and Meta-analysis. *JAMA Oncol.* 2019;5(7):1008-19.
55. Bellmunt J, de Wit R, Vaughn DJ, Fradet Y, Lee JL, Fong L, et al. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. *The New England journal of medicine.* 2017;376(11):1015-26.
56. Powles T, Duran I, van der Heijden MS, Loriot Y, Vogelzang NJ, De Giorgi U, et al. Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial. *Lancet.* 2018;391(10122):748-57.
57. Herbst RS, Baas P, Kim DW, Felip E, Perez-Gracia JL, Han JY, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet.* 2016;387(10027):1540-50.
58. Barlesi F, Vansteenkiste J, Spigel D, Ishii H, Garassino M, de Marinis F, et al. Avelumab versus docetaxel in patients with platinum-treated advanced non-small-cell lung cancer

(JAVELIN Lung 200): an open-label, randomised, phase 3 study. *Lancet Oncol.* 2018;19(11):1468-79.
59. Gandhi L, Rodriguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, et al. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. *The New England journal of medicine.* 2018;378(22):2078-92.
60. Papadimitrakopoulou V, Cobo M, Bordoni Ra, Dubray-Longeras P, Szalai Z, Ursol G, et al. IMpower132: PFS and safety results with 1L atezolizumab+ carboplatin/cisplatin+ pemetrexed in stage IV non-squamous NSCLC. *J Thorac Oncol.* 2018;13(10):S332-S3.
61. Paz-Ares L, Luft A, Vicente D, Tafreshi A, Gumus M, Mazieres J, et al. Pembrolizumab plus Chemotherapy for Squamous Non-Small-Cell Lung Cancer. *The New England journal of medicine.* 2018;379(21):2040-51.
62. Jotte R, Cappuzzo F, Vynnychenko I, Stroyakovskiy D, Rodriguez-Abreu D, Hussein M, et al. Atezolizumab in Combination With Carboplatin and Nab-Paclitaxel in Advanced Squamous NSCLC (IMpower131): Results From a Randomized Phase III Trial. *J Thorac Oncol.* 2020.
63. Nishino M, Giobbie-Hurder A, Hatabu H, Ramaiya NH, and Hodi FS. Incidence of Programmed Cell Death 1 Inhibitor-Related Pneumonitis in Patients With Advanced Cancer: A Systematic Review and Meta-analysis. *JAMA Oncol.* 2016;2(12):1607-16.
64. Ma K, Lu Y, Jiang S, Tang J, Li X, and Zhang Y. The Relative Risk and Incidence of Immune Checkpoint Inhibitors Related Pneumonitis in Patients With Advanced Cancer: A Meta-Analysis. *Front Pharmacol.* 2018;9:1430.
65. Anscher MS, Arora S, Weinstock C, Lubitz R, Amatya A, Fiero M, et al.: American Society of Clinical Oncology; 2020.
66. Robinson DR, Wu YM, Lonigro RJ, Vats P, Cobain E, Everett J, et al. Integrative clinical genomics of metastatic cancer. *Nature.* 2017;548(7667):297-303.
67. Teply BA, and Antonarakis ES. Treatment strategies for DNA repair-deficient prostate cancer. *Expert Rev Clin Pharmacol.* 2017;10(8):889-98.
68. Wu YM, Cieslik M, Lonigro RJ, Vats P, Reimers MA, Cao X, et al. Inactivation of CDK12 Delineates a Distinct Immunogenic Class of Advanced Prostate Cancer. *Cell.* 2018;173(7):1770-82 e14.
69. Reimers MA, Yip SM, Zhang L, Cieslik M, Dhawan M, Montgomery B, et al. Clinical Outcomes in Cyclin-dependent Kinase 12 Mutant Advanced Prostate Cancer. *European urology.* 2020;77(3):333-41.
70. Antonarakis ES, Isaacsson Velho P, Fu W, Wang H, Agarwal N, Sacristan Santos V, et al. CDK12-Altered Prostate Cancer: Clinical Features and Therapeutic Outcomes to Standard Systemic Therapies, Poly (ADP-Ribose) Polymerase Inhibitors, and PD-1 Inhibitors. *JCO Precis Oncol.* 2020;4:370-81.
71. Schweizer MT, Ha G, Gulati R, Brown LC, McKay RR, Dorff T, et al. CDK12-mutated prostate cancer: Clinical outcomes with standard therapies and immune checkpoint blockade. *JCO Precision Oncology.* 2020;4:382-92.
72. Chila R, Guffanti F, and Damia G. Role and therapeutic potential of CDK12 in human cancers. *Cancer Treat Rev.* 2016;50:83-8.
73. Joshi PM, Sutor SL, Huntoon CJ, and Karnitz LM. Ovarian cancer-associated mutations disable catalytic activity of CDK12, a kinase that promotes homologous recombination

repair and resistance to cisplatin and poly(ADP-ribose) polymerase inhibitors. *The Journal of biological chemistry.* 2014;289(13):9247-53.
74. Popova T, Manie E, Boeva V, Battistella A, Goundiam O, Smith NK, et al. Ovarian Cancers Harboring Inactivating Mutations in CDK12 Display a Distinct Genomic Instability Pattern Characterized by Large Tandem Duplications. *Cancer research.* 2016;76(7):1882-91.
75. Grasso CS, Wu YM, Robinson DR, Cao X, Dhanasekaran SM, Khan AP, et al. The mutational landscape of lethal castration-resistant prostate cancer. *Nature.* 2012;487(7406):239-43.
76. Herrera-Abreu MT, Palafox M, Asghar U, Rivas MA, Cutts RJ, Garcia-Murillas I, et al. Early Adaptation and Acquired Resistance to CDK4/6 Inhibition in Estrogen Receptor-Positive Breast Cancer. *Cancer research.* 2016;76(8):2301-13.
77. Mouw KW, Goldberg MS, Konstantinopoulos PA, and D'Andrea AD. DNA Damage and Repair Biomarkers of Immunotherapy Response. *Cancer Discov.* 2017;7(7):675-93.
78. Minciacchi VR, Zijlstra A, Rubin MA, and Di Vizio D. Extracellular vesicles for liquid biopsy in prostate cancer: where are we and where are we headed? *Prostate Cancer Prostatic Dis.* 2017;20(3):251-8.
79. Adalsteinsson VA, Ha G, Freeman SS, Choudhury AD, Stover DG, Parsons HA, et al. Scalable whole-exome sequencing of cell-free DNA reveals high concordance with metastatic tumors. *Nature communications.* 2017;8(1):1324.
80. Annala M, Vandekerkhove G, Khalaf D, Taavitsainen S, Beja K, Warner EW, et al. Circulating Tumor DNA Genomics Correlate with Resistance to Abiraterone and Enzalutamide in Prostate Cancer. *Cancer Discov.* 2018;8(4):444-57.
81. Scher HI, Morris MJ, Stadler WM, Higano C, Basch E, Fizazi K, et al. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2016;34(12):1402-18.
82. Culver BH. How should the lower limit of the normal range be defined? *Respir Care.* 2012;57(1):136-45; discussion 43-5.
83. Lee DW, Santomasso BD, Locke FL, Ghobadi A, Turtle CJ, Brudno JN, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. *Biol Blood Marrow Transplant.* 2019;25(4):625-38.
84. Rotz SJ, Leino D, Szabo S, Mangino JL, Turpin BK, and Pressey JG. Severe cytokine release syndrome in a patient receiving PD-1-directed therapy. *Pediatr Blood Cancer.* 2017;64(12).
85. Adashek ML, and Feldman M. Cytokine Release Syndrome Resulting From Anti-Programmed Death-1 Antibody: Raising Awareness Among Community Oncologists. *J Oncol Pract.* 2019;15(9):502-4.
86. Merad M, and Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. *Nat Rev Immunol.* 2020;20(6):355-62.
87. Riegler LL, Jones GP, and Lee DW. Current approaches in the grading and management of cytokine release syndrome after chimeric antigen receptor T-cell therapy. *Ther Clin Risk Manag.* 2019;15:323-35.
88. McClain KL, and Eckstein O. UpToDate, Waltham, MA, USA; 2018.

89. Ravelli A, Minoia F, Davì S, Horne A, Bovis F, Pistorio A, et al. 2016 Classification Criteria for Macrophage Activation Syndrome Complicating Systemic Juvenile Idiopathic Arthritis: A European League Against Rheumatism/American College of Rheumatology/Paediatric Rheumatology International Trials Organisation Collaborative Initiative. *Ann Rheum Dis.* 2016;75(3):481-9.
90. La Rosée P. Treatment of hemophagocytic lymphohistiocytosis in adults. *Hematology Am Soc Hematol Educ Program.* 2015;2015:190-6.
91. Schram AM, and Berliner N. How I treat hemophagocytic lymphohistiocytosis in the adult patient. *Blood.* 2015;125(19):2908-14.
92. La Rosée P, Horne A, Hines M, von Bahr Greenwood T, Machowicz R, Berliner N, et al. Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. *Blood.* 2019;133(23):2465-77.
93. Kalluri R, and LeBleu VS. The biology, function, and biomedical applications of exosomes. *Science.* 2020;367(6478).
94. Rao A. *International Society of Extracellular Vesicles 2020 Annual Meeting*.
95. Sill MW, Rubinstein L, Litwin S, and Yothers G. A method for utilizing co-primary efficacy outcome measures to screen regimens for activity in two-stage Phase II clinical trials. *Clin Trials.* 2012;9(4):385-95.
96. Davidsson S, Ohlson AL, Andersson SO, Fall K, Meisner A, Fiorentino M, et al. CD4 helper T cells, CD8 cytotoxic T cells, and FOXP3(+) regulatory T cells with respect to lethal prostate cancer. *Mod Pathol.* 2013;26(3):448-55.

APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*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. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B MULTI-CENTER GUIDELINES

B-1. INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for conducting a DF/HCC Multi-Center research protocol. The DF/HCC DSMP serves as a reference for any sites external to DF/HCC that are participating in a DF/HCC clinical trial.

B-1.1 Purpose

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center Multi-Center protocol will comply with Federal Regulations, Health Insurance Portability and Accountability Act (HIPAA) requirements and applicable DF/HCC Policies and Operations.

B-2. GENERAL ROLES AND RESPONSIBILITIES

For DF/HCC Multi-Center Protocols, the following general responsibilities apply, in addition to those outlined in DF/HCC Policies for Sponsor-Investigators:

B-2.1 Coordinating Center

The Coordinating Center is the entity that provides administrative support to the DF/HCC Sponsor in order that he/she may fulfill the responsibilities outlined in the protocol document and DSMP, and as specified in applicable regulatory guidelines (i.e. CTEP Multi-Center Guidelines).

The general responsibilities of the Coordinating Center may include but are not limited to:

- *Assist in protocol development.*
- Maintain FDA correspondence, as applicable.
- *Review registration materials for eligibility and register participants from Participating Institutions in the DF/HCC clinical trial management system (CTMS).*
- *Distribute protocol and informed consent document updates to External Sites as needed.*
- *Oversee the data collection process from External Sites.*
- *Maintain documentation of Serious Adverse Event (SAE) reports and deviations/violation submitted by External Sites and provide to the DF/HCC Sponsor for timely review and submission to the IRB of record, as necessary.*
- *Distribute serious adverse events reported to the DF/HCC Sponsor that fall under the reporting requirements for the IRB of record to all External Sites.*
- *Provide External Sites with information regarding DF/HCC requirements that they will be expected to comply with.*
- *Carry out plan to monitor External Sites either by on-site or remote monitoring.*
- *Maintain Regulatory documents of all External Sites which includes but is not limited to the following: local IRB approvals/notifications from all External Sites,*

confirmation of Federalwide Assurances (FWAs) for all sites, all SAE submissions, Screening Logs for all sites, IRB approved consents for all sites

- *Conduct regular communications with all External Sites (conference calls, emails, etc) and maintain documentation all relevant communications.*

B-2.2 External Site

An External Site is an institution that is outside the DF/HCC and DF/PCC consortium that is collaborating with DF/HCC on a protocol where the sponsor is a DF/HCC investigator. The External Site acknowledges the DF/HCC Sponsor as having the ultimate authority and responsibility for the overall conduct of the study.

Each External Site is expected to comply with all applicable DF/HCC requirements stated within this Data and Safety Monitoring Plan and/or the protocol document.

The general responsibilities for each External Site may include but are not limited to:

- *Document the delegation of research specific activities to study personnel.*
- *Commit to the accrual of participants to the protocol.*
- *Submit protocol and/or amendments to their IRB of record. For studies under a single IRB, the Coordinating Center will facilitate any study-wide submissions.*
- *Maintain regulatory files as per ICH GCP and federal requirements.*
- *Provide the Coordinating Center with regulatory documents or source documents as requested.*
- *Participate in protocol training prior to enrolling participants and throughout the trial as required.*
- *Update Coordinating Center with research staff changes on a timely basis.*
- *Register participants through the Coordinating Center prior to beginning research related activities when required by the sponsor.*
- *Submit Serious Adverse Event (SAE) reports to sponsor, Coordinating Center, and IRB of record as applicable, in accordance with DF/HCC requirements.*
- *Submit protocol deviations and violations to the Sponsor, Coordinating Center, and IRB of record as applicable..*
- *Order, store and dispense investigational agents and/or other protocol mandated drugs per federal guidelines and protocol requirements.*
- *Participate in any quality assurance activities and meet with monitors or auditors at the conclusion of a visit to review findings.*
- *Promptly provide follow-up and/or corrective action plans for any monitoring queries or audit findings.*
- *Notify the sponsor immediately of any regulatory authority inspection of this protocol at the External Site.*

B-3. DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

Certain DF/HCC Policy requirements apply to External Sites participating in DF/HCC research. The following section will clarify DF/HCC requirements and further detail the expectations for participating in a DF/HCC Multi-Center protocol.

B-3.1 Protocol Revisions and Closures

The External Sites will receive notification of protocol revisions and closures from the Coordinating Center. When under a separate IRB, it is the individual External Site's responsibility to notify its IRB of these revisions.

- ***Protocol revisions:*** *External Sites will receive written notification of protocol revisions from the Coordinating Center. All protocol revisions should be IRB approved and implemented within a timely manner from receipt of the notification.*

- ***Protocol closures and temporary holds:*** *External Sites will receive notification of protocol closures and temporary holds from the Coordinating Center. Closures and holds will be effective immediately. In addition, the Coordinating Center, will update the External Sites on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.*

B-3.2 Informed Consent Requirements

The DF/HCC approved informed consent document will serve as a template for the informed consent for External Sites. The External Site consent form must follow the consent template as closely as possible and should adhere to specifications outlined in the DF/HCC Guidance Document on Model Consent Language for Investigator-Sponsored Multi-Center Trials. This document will be provided separately to each External Site upon request.

External Sites must send their version of the informed consent document to the Coordinating Center for sponsor review and approval. If the HIPAA authorization is a separate document, please submit to the sponsor for the study record. Once sponsor approval is obtained, the External site may submit to their IRB of record, as applicable. In these cases, the approved consent form must also be submitted to the Coordinating Center after approval by the local IRB for all consent versions.

The Principal Investigator (PI) at each External Site will identify the appropriate members of the study team who will be obtaining consent and signing the consent form for protocols. External Sites must follow the DF/HCC requirement that for all interventional drug, biologic, or device research, only attending physicians may obtain initial informed consent and any re-consent that requires a full revised consent form.

B-3.3 IRB Re-Approval

Verification of IRB re-approval for the External Sites is required in order to continue research activities. There is no grace period for continuing approvals.

The Coordinating Center will not register participants if a re-approval letter is not received for the External Site on or before the anniversary of the previous approval date.

B-3.4 DF/HCC Multi-Center Protocol Confidentiality

All documents, investigative reports, or information relating to the participant are strictly confidential. Whenever reasonably feasible, any participant specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the Coordinating Center should be de-identified. It is recommended that the assigned protocol case number be used for all participant specific documents. Participant initials may be included or retained for cross verification of identification.

B-3.5 Participant Registration and Randomization

To register a participant, the following documents should be completed by the External Site and e-mailed to the Coordinating Center:

- Current IRB approved informed consent document informed consent document signed by participant and investigator. Participant name and MRN must be redacted. Please ensure the participant's initials are written on each page of the informed consent document.
- HIPAA authorization form (if separate from the informed consent document)
- Signed and dated Eligibility Checklist
- The following source documentation is required:
    - Documentation of prior treatments/procedures performed to treat RCC
    - Reports documenting disease status
        - Chest CT
        - CT or MRI Abdomen and Pelvis
        - Tc99m Bone Scan
    - Pathology Report
    - Concomitant medication list
    - Progress note or equivalent documentation of consenting visit
    - Progress note documenting medical history and oncologic history
    - Screening Labs
    - Screening visit note with vital signs, weight, height, ECOG performance status, physical examination

The Coordinating Center will review the submitted documents in order to verify eligibility and consent. To complete the registration process, the Coordinating Center will:

- Register the participant on the study with the DF/HCC Clinical Trial Management System (CTMS).

- Upon receiving confirmation of registration, the Coordinating Center will inform the External Site and provide the study specific participant case number, and, if applicable, assigned treatment and/or dose level.

At the time of registration, the following identifiers are required for all subjects: initials, date of birth, gender, race and ethnicity. Once eligibility has been established and the participant successfully registered, the participant is assigned a unique protocol case number. External Sites should submit all de-identified subsequent communication and documents to the Coordinating Center, using this case number to identify the subject.

B-3.6 Initiation of Therapy

Participants must be registered with the DF/HCC CTMS before the initiation of treatment or other protocol-specific interventions. Treatment and other protocol-specific interventions may not be initiated until the External Site receives confirmation of the participant's registration from the Coordinating Center. The DF/HCC Sponsor and IRB of record must be notified of any violations to this policy.

B-3.7 Eligibility Exceptions

No exceptions to the eligibility requirements for a protocol without IRB approval will be permitted. All External Sites are required to fully comply with this requirement. The process for requesting an eligibility exception is defined below.

B-3.8 Data Management

DF/HCC develops case report forms (CRF/eCRFs), for use with the protocol. These forms are designed to collect data for each study. DF/HCC provides a web based training for all eCRF users.

B-3.9 Data Forms Review

Data submissions are monitored for timeliness and completeness of submission. If study forms are received with missing or questionable data, the submitting institution will receive a written or electronic query from the DF/HCC Office of Data Quality, Coordinating Center, or designee.

Responses to all queries should be completed and submitted within 14 calendar days.

If study forms are not submitted on schedule, the External Sites will periodically receive a Missing Form Report from the Coordinating Center noting the missing forms.

B-3.9 Protocol Reporting Requirements

B-3.9.1 Protocol Deviations, Exceptions and Violations

Federal Regulations require an IRB to review proposed changes in a research activity to ensure that researchers do not initiate changes in approved research without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the participant. DF/HCC requires all departures from the defined procedures set forth in the IRB approved protocol to be reported to the DF/HCC Sponsor and to the IRB of record.

B-3.9.2 Reporting Procedures

Requests to deviate from the protocol require approval from the IRB of record and the sponsor.

All protocol violations must be sent to the Coordinating Center in a timely manner. The Coordinating Center will provide training for the requirements for the reporting of violations.

B-3.9.3 Guidelines for Processing IND Safety Reports

The DF/HCC Sponsor will review all IND Safety Reports per DF/HCC requirements, and ensure that all IND Safety Reports are distributed to the External Sites as required by DF/HCC Policy. External Sites will review/submit to the IRB according to their institutional policies and procedures.

B-4. MONITORING: QUALITY CONTROL

The Coordinating Center, with the aid of the DF/HCC Office of Data Quality, provides quality control oversight for the protocol.

B-4.1 Ongoing Monitoring of Protocol Compliance

The External Sites may be required to submit participant source documents to the Coordinating Center for monitoring. External Sites may also be subject to on-site monitoring conducted by the Coordinating Center.

The Coordinating Center will implement ongoing monitoring activities to ensure that External Sites are complying with regulatory and protocol requirements, data quality, and participant safety. Monitoring practices may include but are not limited to source data verification, and review and analysis of eligibility requirements, informed consent procedures, adverse events and all associated documentation, review of study drug administration/treatment, regulatory files, protocol departures reporting, pharmacy records, response assessments, and data management.

Site visits will generally occur once a year for sites that are actively enrolling participants and have participants in treatment. Additional monitoring activities may occur if incidences

of non-compliance are discovered or at the request of the DF/HCC Sponsor. Virtual monitoring (source documents are sent to DFCI for review) may be performed in lieu of a site visit if the study staff and PI determine that virtual monitoring is appropriate for the site. The decision to perform virtual monitoring in lieu of a site visit will be based upon the site's enrollment, study compliance history, history collaborating with DFCI on other multi-center studies, and number of participants in active treatment.

Monitoring will occur before the clinical phase of the protocol begins and will continue during protocol performance through study completion.

Teleconferences between DFCI and the participating sites will be conducted on approximately a monthly basis. Meeting minutes for teleconferences will be issued to all participating sites. Site initiation visits will be conducted via teleconference. Ongoing training will also be conducted via teleconference as needed. The Coordinating Center, Dana Farber Cancer Institute will be available to all participating sites for resolving questions, concerns and facilitating compliance.

B-4.2 Monitoring Reports

The DF/HCC Sponsor will review all monitoring reports to ensure protocol compliance. The DF/HCC Sponsor may increase the monitoring activities at External Sites that are unable to comply with the protocol, DF/HCC Sponsor requirements or federal and local regulations.

B-4.3 Accrual Monitoring

Prior to extending a protocol to an external site, the DF/HCC Sponsor will establish accrual requirements for each External Site. Accrual will be monitored for each External Site by the DF/HCC Sponsor or designee. Sites that are not meeting their accrual expectations may be subject to termination.

The following **minimum** accrual requirements are recommended:

1) Phase I: 2 per site/annually
2) Phase II-III: 3 per site/annually. However, given the additional regulatory burden and cost of overseeing each site, a consideration of 5 per site/annually should be a minimum target for each site..
3) Note: Diseases that are extremely rare may have accrual expectations of 0-1 accruals/year.]

B-5. AUDITING: QUALITY ASSURANCE

B-5.1 DF/HCC Internal Audits

All External Sites are subject to audit by the DF/HCC Office of Data Quality (ODQ). Typically, approximately 3-4 participants would be audited at the site over a 2-day period. If violations which impact participant safety or the integrity of the study are found, more participant records may be audited.

B-5.2 Audit Notifications

It is the External Site's responsibility to notify the Coordinating Center of all external audits or inspections (e.g., FDA, EMA, NCI) that involve this protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the Coordinating Center, within 12 weeks after the audit date.

B-5.3 Audit Reports

The DF/HCC Sponsor will review all final audit reports and corrective action plans, if applicable. The Coordinating Center, must forward any reports to the DF/HCC ODQ per DF/HCC policy for review by the DF/HCC Audit Committee. For unacceptable audits, the DF/HCC Audit Committee would forward the final audit report and corrective action plan to the IRB as applicable.

B-5.4 External Site Performance

The DF/HCC Sponsor and the IRB of record are charged with considering the totality of an institution's performance in considering institutional participation in the protocol.

External Sites that fail to meet the performance goals of accrual, submission of timely and accurate data, adherence to protocol requirements, and compliance with state and federal regulations, may be put on hold or closed.

Appendix C
Safety Reporting Fax Cover Sheet

Genentech
A Member of the Roche Group

SAFETY REPORTING FAX COVER SHEET

GENENTECH SUPPORTED RESEARCH

AE / SAE FAX No: (650) 238-6067

Genentech Study Number	
Principal Investigator	
Site Name	
Reporter name	
Reporter Telephone #	
Reporter Fax #	

Initial Report Date	[DD] / [MON] / [YY]
Follow-up Report Date	[DD] / [MON] / [YY]

Subject Initials (Enter a dash if patient has no middle name)	[ ] - [ ] - [ ]

SAE or Safety Reporting questions, contact Genentech Drug Safety: (888) 835-2555

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET

Appendix D
Content Required in the Line Listing Used for Exchange of Single Case Reports

Note to the author: Appendix D is only applicable when Single Case Reports are exchanged via monthly Line Listing.

The following fields must be populated in the Line Listing by the Sponsor-Investigator in order for Roche to process the Single Case Reports:

- Protocol number
- Patient number
- Date of birth
- Patient initials, as applicable
- Primary reporter country (and country of occurrence of event if different to that of primary reporter)
- AE term and/or Medical Dictionary for Regulatory Activities (MedDRA) term
- Seriousness of event and seriousness criteria
- Medical History and concomitant medications
- Onset date and end date (if applicable) of event
- Death date and cause (if applicable)
- Study drugs received
- First and last dose dates, dosage, frequency and indication of the suspected drug
- Cause(s) of event - Roche Medicinal Product
- Cause(s) of event - other study drugs attribution (to be specified) and other attributions (to be specified)
- Common Terminology Criteria for Adverse Events (CTCAE) Grade
- AE Event description
- AE Event outcome
- Action taken
- Batch Lot number if biological products

Appendix E
Preexisting Autoimmune Diseases and Immune Deficiencies

Patients should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Patients with any history of immune deficiencies or autoimmune disease listed in the table below are excluded from participating in the study. Possible exceptions to this exclusion could be patients with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g., acute Lyme arthritis). Caution should be used when considering atezolizumab for patients who have previously experienced a severe or life–threatening skin adverse reaction while receiving another immunostimulatory anti-cancer agent.

Autoimmune Diseases and Immune Deficiencies

• Acute disseminated encephalomyelitis • Addison disease • Ankylosing spondylitis • Antiphospholipid antibody syndrome • Aplastic anemia • Autoimmune hemolytic anemia • Autoimmune hepatitis • Autoimmune hypoparathyroidism • Autoimmune hypophysitis • Autoimmune myelitis • Autoimmune myocarditis • Autoimmune oophoritis • Autoimmune orchitis • Autoimmune thrombocytopenic purpura • Behçet disease • Bullous pemphigoid • Chronic fatigue syndrome • Chronic inflammatory demyelinating polyneuropathy • Churg-Strauss syndrome • Crohn disease	• Dermatomyositis • Diabetes mellitus type 1 • Dysautonomia • Epidermolysis bullosa acquisita • Gestational pemphigoid • Giant cell arteritis • Goodpasture syndrome • Graves disease • Guillain-Barré syndrome • Hashimoto disease • IgA nephropathy • Inflammatory bowel disease • Interstitial cystitis • Kawasaki disease • Lambert-Eaton myasthenia syndrome • Lupus erythematosus • Lyme disease, chronic • Meniere syndrome • Mooren ulcer • Morphea • Multiple sclerosis • Myasthenia gravis	• Neuromyotonia • Opsoclonus myoclonus syndrome • Optic neuritis • Ord thyroiditis • Pemphigus • Pernicious anemia • Polyarteritis nodosa • Polyarthritis • Polyglandular autoimmune syndrome • Primary biliary cholangitis • Psoriasis • Reiter syndrome • Rheumatoid arthritis • Sarcoidosis • Scleroderma • Sjögren syndrome • Stiff-Person syndrome • Takayasu arteritis • Ulcerative colitis • Vitiligo • Vogt-Koyanagi-Harada disease • Wegener granulomatosis

Appendix F
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.