UCSF Helen Diller Family Comprehensive Cancer Center

A Phase 2 Study of Apalutamide Plus Cetrelimab in Patients with Treatment-Emergent Small Cell Neuroendocrine Prostate Cancer

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Protocol Signature Page

1. I agree to follow this protocol version as approved by the UCSF Protocol Review and Monitoring Committee (PRMC), Institutional Review Board (IRB), and Data and Safety Monitoring Committee (DSMC).
2. I will conduct the study in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practices (GCP) and the applicable IRB, ethical, federal, state, and local regulatory requirements.
3. I certify that I, and the study staff, have received the required training to conduct this research protocol.
4. I agree to maintain adequate and accurate records in accordance with IRB policies, federal, state and local laws and regulations.

UCSF Principal Investigator

_____
Printed Name

_____ _____
Signature Date

Abstract

Title	A Phase 2 Study of Apalutamide Plus Cetrelimab in Patients with Treatment-Emergent Small Cell Neuroendocrine Prostate Cancer
Study Description	Phase 2 single arm, Simon two stage evaluation of the combination of apalutamide plus cetrelimab in patients with mCRPC and histologic and/or genomic evidence of treatment-emergent small cell neuroendocrine prostate cancer who have previously progressed on at least one prior androgen signaling inhibitor. The primary study endpoint is composite response rate as defined by PSA50 response and/or objective response by RECIST 1.1 criteria.
Phase of Study	Phase 2
Investigational Products	Apalutamide, Cetrelimab
Study population	Male, adult (18 years of age and older) patients with metastatic castration resistant prostate cancer (mCRPC) with disease progression (PD) on at least one second generation androgen signaling inhibitor, including abiraterone acetate, apalutamide, darolutamide, and/or enzalutamide and evidence of treatment-emergent small cell neuroendocrine cancer (t-SCNC). All races/ethnicity are included.
Primary Objective	To determine the composite response rate as defined by achieving one or more of the following at any time point during study treatment: • PSA50, decline from baseline in serum PSA of ≥ 50%, confirmed by repeat measurement ≥ 4 weeks later • Objective response by RECIST 1.1 criteria
Secondary Objectives	1. To determine safety of the combination as determined by CTCAE version 5.0 2. To determine the median radiographic progression-free survival by PCWG3 criteria 3. To determine the PSA50 and PSA90 response proportion achieved 4. To determine the median PSA progression-free survival 5. To determine the median overall survival 6. To determine the objective response rate and median duration of response by RECIST 1.1 criteria
Sample Size	N = 24 patients.

Duration of Study Treatment	Participants may continue study treatment from the time of treatment initiation until confirmed radiographic PD per PCWG3/RECIST 1.1 criteria, unequivocal clinical progression, unacceptable toxicity, or patient withdrawal, whichever occurs first – for a maximum of 24 months.
Duration of Follow Up	Safety Follow up: 30 days Safety Follow-up: 100 days Long Term / Survival Follow up: Patients will be followed for overall survival every 90 days (+/- 30 days) from last dose of study treatment, until death, withdrawal of consent, or the end of the study, whichever occurs first.

List of Abbreviations

ADT	androgen deprivation therapy
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AR	androgen receptor
ARPI	androgen receptor pathway inhibitors
AST	aspartate aminotransferase
BET	Bromodomain extraterminal protein
BUN	blood urea nitrogen
CBC	complete blood cell (count)
CNS	central nervous system
CR	complete response
CRF	case report form
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical Trial Management System
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
ECG/EKG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	glomerular filtration rate
HBV	hepatitis B virus
HCV	hepatitis C virus
HDFCCC	Helen Diller Family Comprehensive Cancer Center
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
IAC	intermediate atypical carcinoma
ICF	informed consent form
ICH	International Conference on Harmonization
IDS	Investigational Drug Services (UCSF)
IND	investigational new drug application
IP	investigational product
IRB	Institutional Review Board
IV	Intravenous

List of Abbreviations

mCPRC	metastatic castration resistant prostate cancer
MRI	magnetic resonance imaging
NCI	National Cancer Institute
PD	disease progression
PD-1	programmed cell death 1
PO	*Per os* (by mouth, orally)
PR	partial response
PRC	Protocol Review Committee (UCSF)
PSA	Prostate Serum Antigen
rPD	Radiographic progressive disease
SD	stable disease
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SLD	Sum of longest diameters
t-SCNC	treatment-emergent small cell neuroendocrine carcinoma

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1 Introduction

1.1 Background

Prostate cancer is the second leading cause of cancer death in men in the Western World, largely driven by patients harboring recurrent or newly diagnosed metastatic disease. These patients have a rapid and favorable response to androgen deprivation therapy (ADT). However, most patients inevitably develop hormone refractory disease, termed metastatic castration resistant prostate cancer (mCRPC). Over the last decade, there has been an expansion of therapies for patients with mCRPC beyond traditional cytotoxic chemotherapies, including novel androgen receptor (AR) pathway inhibitors (ARPI) that more completely ablate androgen signaling such as abiraterone acetate, enzalutamide, and apalutamide (Beer et al., 2014; de Bono et al., 2011; Fizazi et al., 2012; Ryan et al., 2015, 2013; Scher et al., 2012; Smith et al., 2018), sipuleucel-T, an autologous cellular immunotherapy targeting prostatic acid phosphatase (PAP) (Kantoff et al., 2010), and radium-223, a bone-targeting alpha emitter (Parker et al., 2013). Despite these therapeutic advances, many patients on mCRPC eventually succumb to their disease, often due to acquired tumor resistance to these novel agents. In particular, there remain few treatment options for men with mCRPC refractory to the ARPI. Therefore, there is a great need to develop clinically efficacious, well-tolerated, novel therapies for this patient population.

1.2 Transdifferentiation is an Adaptive Response to Long-term ADT

There is marked heterogeneity across mCRPC patients with widely varying clinical outcomes and therapeutic responses driven largely from diverse mechanisms of resistance to overcome androgen-signaling inhibition. Transdifferentiation to a neuroendocrine phenotype, termed treatment-emergent small cell neuroendocrine prostate cancer (t-SCNC), represents a highly aggressive and lethal subset of prostate cancer that is becoming increasingly common in previously treated mCRPC. While *de novo* SCNC represent 1-2% of new cases, in our prospective, multi-institutional study of over 200 unselected mCRPC patients previously treated with ARPI, treatment-emergent SCNC (t-SCNC) was identified in 17% of mCRPC biopsies (Aggarwal et al., 2018). Compared to mCRPC with adenocarcinoma features, t-SCNC is characterized by decreased AR signaling, enrichment for loss of *RB1* and *TP53*, and enrichment of activation of transcriptional factors including EZH2, POU3F2, ASCL1, among others.

It is hypothesized that t-SCNC arise clonally from adenocarcinoma, though through which molecular mechanisms, i.e. de-differentiation to a primitive progenitor or transdifferentiation from epithelial to neuronal phenotypes, remains under active investigation (Aggarwal et al., 2019; Beltran et al., 2016; Guo et al., 2011; Zou et al., 2017). Importantly, patients with t-SCNC exhibit poor prognoses compared to mCRPC with adenocarcinoma (Aggarwal et al., 2018; Small et al., 2016). Furthermore, patients with t-SCNC have limited effective treatment options outside of traditional platinum-based chemotherapies, which itself have limited durability of response and carry significant risk of undesired side effects (Aparicio et al., 2013). In the Aparicio et al. study, 97% of patients treated with platinum therapy experienced progression of disease with a median time of 3.0 months. Therefore, there is an unmet clinical need to develop new, durable therapies for these two high-risk mCRPC subtypes.

Identification of t-SCNC currently relies on histologic evaluation of a metastatic tumor biopsy, which can be difficult to obtain in patients owing to the sclerotic nature of this bone-tropic disease entity. Contrary to the classic clinical characteristics of *de novo* t-SCNC, the presence of visceral metastases or elevation of serum neuroendocrine markers does not reliably identify t-SCNC on paired tumor biopsies. Several clinical and/or genomic hallmarks enrich for the identification of t-SCNC, including the presence of *RB1* genomic loss on somatic tumor profiling, as well as the presence of low PSA secretion in relation to metastatic disease burden.

Among 183 evaluable patients, low PSA secretion (PSA < 5 ng/mL) with concomitant high metastatic disease burden (> 5 metastases on conventional imaging) was found in 15 patients (8%) and was associated with enrichment for t-SCNC transcriptional signature, low AR transcriptional activity. *RB1* genomic loss is enriched in t-SCNC vs. adenocarcinoma biopsies (Aggarwal et al. JCO 2018) and is likewise associated with significant shortened survival (Chen et al. Eur Urol 2019).

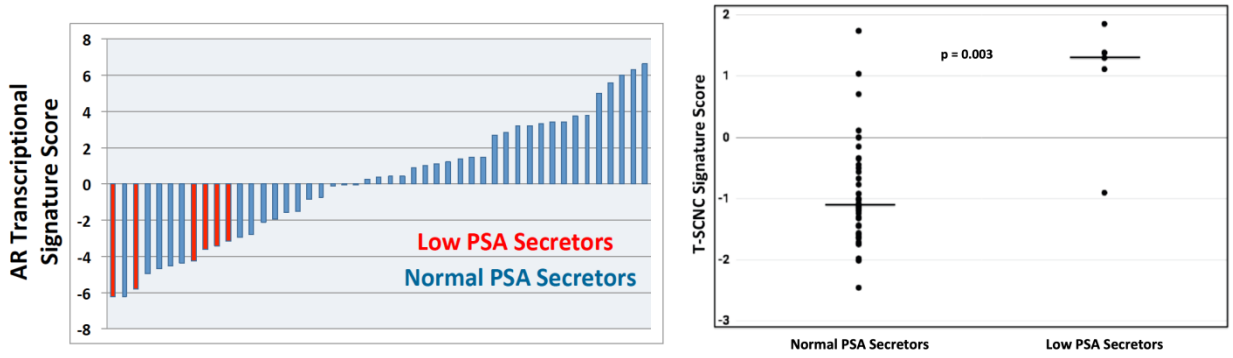

Figure 1.2 AR Transcriptional Signature Score and T-SCNC Signature Score

1.3 Activity of Immune Checkpoint Inhibition in Unselected mCRPC Alone and in Combination with AR Pathway Inhibition

In patients with unselected mCRPC, pembrolizumab has modest anti-tumor activity, but durable responses can be achieved in a minority of patients. In the recently reported updated analysis of the KEYNOTE-199 study of mCRPC patients who had previously received docetaxel, the objective response rate in patients with measurable disease was 5% and 3% in those with PD-L1 positive and negative tumors, respectively (Antonarakis et al. 2019). Duration of responses lasting ≥ 12 months was 71% and 50%, respectively, in the two cohorts. The PSA50 response rate was 11% overall, and there did not appear to be an enrichment of response in PD-L1 positive vs. negative tumors.

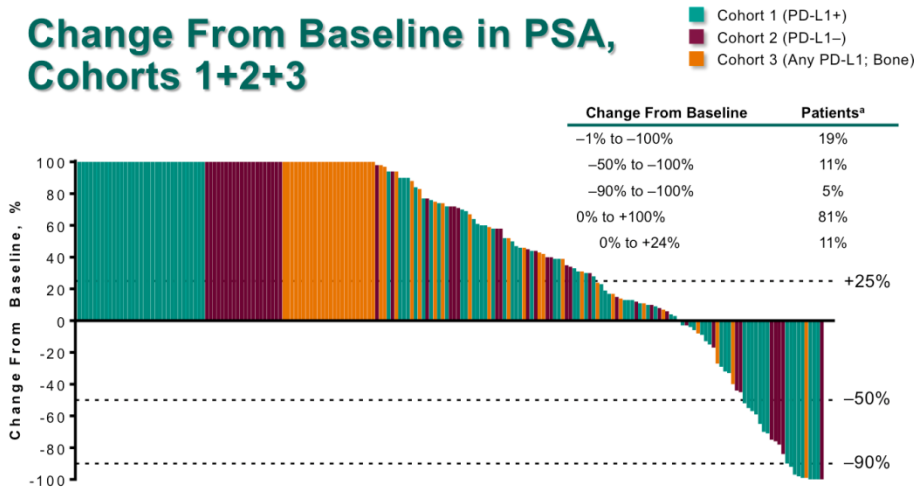

Figure 1.3 Change from Baseline in PSA, Cohorts 1+2+3

Pembrolizumab combined with AR targeted therapy may lead to increased response rate however this has not been definitively demonstrated in a randomized trial setting. In a single arm study (KEYNOTE-365, Cohort C) of pembrolizumab plus enzalutamide in abiraterone

acetate-resistant, chemotherapy-naïve mCRPC, the PSA50 response rate was 27% (18/67 patients), and the objective response rate was 20% (5/25 patients with measurable disease) (Fong P, et al. 2019).

1.4 Immunogenicity of t-SCNC compared to adenocarcinoma without neuroendocrine features and clinical activity of immune checkpoint blockade in high grade neuroendocrine cancers

The immunogenicity of mCRPC tumors, including the mutation burden, tumor infiltrating lymphocytes, and expression of T-cell regulatory checkpoint molecules like PD-1 and PD-L1 are low in an unselected population of prostate tumors compared to other tumor types that show a higher response rate to checkpoint blockade, like melanoma (Haffner et al., 2018). PD-L1 expression strongly correlates with objective response to anti-PD-1 therapy (Taube et al., 2014). However, only 14% of mCRPC patients in the KEYNOTE-028 study examining pembrolizumab in this patient population screened positive for PD-L1 expression. Recent work has demonstrated that PD-L1 expression was higher in patients with t-SCNC compared to mCRPC without evidence of neuroendocrine features (Ferguson et al., 2019; Nappi et al., 2019). This suggests that de-differentiated t-SCNC have increased immunogenicity and may have a better response rate to anti-PD-1 therapy compared to mCRPC cases without neuroendocrine features.

The efficacy of immune checkpoint inhibition in high grade neuroendocrine cancers is supported by recent clinical efficacy and accelerated FDA approval for nivolumab in small cell lung cancer (Antonia et al. Lancet Oncology 2016). An objective response was achieved in ten (10%) of 98 patients receiving nivolumab 3 mg/kg, one (33%) of three patients receiving nivolumab 1 mg/kg plus ipilimumab 1 mg/kg, 14 (23%) of 61 receiving nivolumab 1 mg/kg plus ipilimumab 3 mg/kg, and ten (19%) of 54 receiving nivolumab 3 mg/kg plus ipilimumab 1 mg/kg.

In extrapulmonary high grade neuroendocrine cancers, immune checkpoint inhibition has shown preliminary evidence of activity. In the neuroendocrine tumor cohort of the basket DART study, the objective response rate with combination of ipilimumab + nivolumab was 44% in the subset of patients with high-grade disease.

1.5 Cetrelimab in Prostate and Other Solid Tumor Malignancies

Cetrelimab (JNJ-63723283) is a fully human immunoglobulin G4 (IgG4) kappa mAb containing the hinge-stabilizing S228P mutation. This mutation prevents the fragment antigen binding (Fab) arm exchange that normally occurs with IgG4 antibodies. Cetrelimab binds to PD-1 with high affinity and specificity, blocks binding to both PD-L1 and PD-L2 ligands, enhances pro-inflammatory cytokine production from ex vivo stimulated T cells, and reduces tumor volume in a number of preclinical models in vivo.

Study 63723283LUC1001 is an ongoing, multicenter, Phase 1/2 FIH study of cetrelimab in subjects with advanced solid tumor malignancies. Part 1 of the study, initiated on 21 November 2016 (date of consent of the first eligible subject), consists of dose escalation cohorts and PK/PD cohorts. Part 1 established the recommended Phase 2 dose (RP2D), which may be administered at either 240 mg once every 2 weeks (q2w) or 480 mg once every 4 weeks (q4w). In Part 2, initiated on 03 May 2017 (date of consent of the first eligible subject), this RP2D is being evaluated in selected solid tumor types, including non-small cell lung cancer (NSCLC), melanoma and high-level microsatellite instability (MSI-H) or mismatch-repair deficiency (dMMR) colorectal cancer (CRC). The purposes of dose expansion in Part 2 are to further characterize the safety and to assess the antitumor activity of the RP2D.

As of the clinical safety and efficacy data cutoff date of 02 September 2019, a total of 204 subjects have received at least 1 dose of cetrelimab. The age of enrolled subjects ranged from

23 to 86 years. The majority of subjects treated with cetrelimab had Stage III or IV malignancy at the time of initial diagnosis and metastatic disease at study entry, consistent with the protocol-specified requirements of metastatic or unresectable advanced cancers. The number of prior regimens of anticancer therapy ranged from 1 to 12, with a median number of 2 prior therapies. As of the clinical safety data cutoff date, the duration of cetrelimab treatment ranged from 1 to 28.5 months, with a median treatment duration of 3.25 months. The number of doses administered ranged from 1 to 63.

The RP2D of 240 mg q2w was determined based on interim safety, PK, and PD data as of 27 April 2017. The additional interim safety, PK and PD data as of September 2017 support an alternate regimen, namely 480 mg q4w, with the same total dose as RP2D of 240 mg q2w but given with a longer dosing interval which enables flexibility of drug administration in various clinical settings. Selection of the RP2D of 240 mg q2w and 480 mg q4w was based on the following:

- No maximum tolerated dose has been identified with administration of doses up to 460 mg q2w and 480 mg q4w and doses were well tolerated (Section 4.4).
- Cetrelimab demonstrated comparable preclinical in vivo TGI and comparable in vitro activity across various assays as the approved PD-1 inhibitors nivolumab and pembrolizumab (Section 3.1.1). Therefore, similar clinical efficacious target concentrations would be expected for cetrelimab.
- Based on preliminary PK data, the median observed near-steady state Cmin for cetrelimab at 240 mg q2w is 44.8 µg/mL (N=5, trough concentration before the fifth dose). This is comparable to the Cmin,ss reported for nivolumab (57 µg/mL7,9) and pembrolizumab (23 µg/mL6,10) at their approved doses (240 mg q2w for nivolumab and 2 mg/kg or 200 mg q3w for pembrolizumab).
- The median steady state Cmin,ss for cetrelimab at 480 mg q4w is expected to be
- approximately 42 µg/mL, based on an observed median Cmin after first dose at 30 µg/mL and predicted accumulation ratio of ~1.4 based on preliminary PK modeling. The Cmin,ss from 240 mg q2w and 480 q2w is therefore expected to be comparable, and in range with other anti-PD-1 agents nivolumab and pembrolizumab at their approved clinical dose.
- Administration of cetrelimab resulted in saturation of PD-1 RO on circulating CD3+ T cells at all administered doses (80 to 480 mg) and dosing frequencies (q2w and q4w).

In subjects receiving the RP2D of 240 mg IV every 2 weeks in the cetrelimab monotherapy study (Study 63723283LUC1001; NCT02908906), the observed ORR (CR+PR) was 21.9% (32/146) in all subjects evaluable for response. Five of the 146 (3.4%) subjects (all with melanoma) demonstrated a complete response (CR) and 27 (18.5%) had a partial response (PR) as assessed by the investigator. Overall, 29 (19.9%) subjects receiving cetrelimab had stable disease (SD).

Overall, 207 (97.2%) of the 213 subjects who received treatment experienced at least 1 TEAE. One hundred forty-two (142, 66.7%) subjects experienced TEAEs considered to be possibly, probably, or very likely related to cetrelimab administration by the investigator. Across all dose cohorts, the most frequently reported TEAEs (≥10% of subjects) were as follows: asthenia (24.4%), fatigue (20.7%), dyspnea (20.2%), pyrexia (19.7%), diarrhea (18.8%), anemia, decreased appetite, and nausea (17.8% each), cough (17.4%), back pain (15.5%), aspartate aminotransferase (AST) increased and vomiting (13.1% each), alanine aminotransferase (ALT) increased (12.7%), abdominal pain (11.7%), constipation (11.3%), and arthralgia and rash

(10.3% each). In the 161 subjects receiving 240 mg q2w, the most frequent TEAEs (≥10% of subjects) were as follows: asthenia (27.9%), dyspnea, diarrhea, and pyrexia (21.8% each), cough (20.0%), fatigue and decreased appetite (18.2% each), anemia (17.6%), nausea (17.0%), ALT increased (15.2%), AST increased (14.5%), and back pain (15.8%).

Overall, Grade 3 or higher TEAEs were experienced by 113 (53.1%) of the 213 subjects in the monotherapy studies (Table 26). The most frequently reported Grade 3 or higher TEAEs (≥2% of subjects) were as follows: anemia (7.0%), dyspnea (5.6%), GGT increased (4.7%), hyponatremia (4.2%), AST increased and hyperamylasemia (3.3% each), ALT increased, hypertension, fatigue and lipase increased (2.8% each), pleural effusion, abdominal pain and general physical health deterioration (2.3% each), and urinary tract infection, neutropenia, blood alkaline phosphatase (ALP) increased, asthenia, and hyperbilirubineamia (1.9%).

Overall, 71 (33.3%) of the 213 subjects treated in the monotherapy studies experienced treatment-emergent irAEs as assessed by the investigator. The most commonly reported irAEs (>2% of subjects) included hypothyroidism (6.1%), rash (4.7%), asthenia (4.2%), hyperthyroidism and dyspnea (3.3% each), pruritus and diarrhea (2.8% each), and pneumonitis (2.3%). Nine (9, 4.2%) subjects experienced irAEs that led to treatment discontinuation: pneumonitis in 3 subjects, and myocarditis, hyperthyroidism, autoimmune colitis, hepatotoxicity, ALT increased, GGT increased, myopathy, and myasthenia gravis in 1 subject each.

PK/PD and immunogenicity data are presented in the Investigational Brochure.

1.6 Combination of Apalutamide Plus Cetrelimab

Study 56021927PCR2032 (NCT03551782) is an ongoing, multicenter, apalutamide Phase 1b study of subjects who currently have mCRPC and who have progressed on therapy with abiraterone acetate plus prednisone/prednisolone (AA-P), apalutamide, or enzalutamide. The study was initiated on 2 July 2018 (date of first subject consent). As of the clinical data cutoff date of 02 September 2019, a total of 27 subjects have received at least 1 dose of apalutamide in combination with cetrelimab. The combination was overall deemed tolerable with no dose-limiting toxicities noted. Grade 3 or higher treatment-emergent adverse events (AEs) included: rash (37.0%), and fatigue/asthenia (14.8%). Overall, AEs leading to treatment discontinuation occurred in 6/27 patients (22.2%), including three patients with rash, one patient with hypersensitivity reaction, one patient with serum sickness, and one patient with asthenia.

1.7 Rationale for the Continuation of Androgen Receptor Blockade in Transdifferentiated Prostate Cancer

Despite the low AR transcriptional activity of treatment-emergent small cell neuroendocrine prostate cancer, there is persistent AR expression observed in the majority of t-SCNC biopsies (Aggarwal et al. JCO 2018). This indicates that epigenetic dysregulation leads to reprogramming away from an AR-driven transcriptional program. Therefore, continuation of AR blockade in the form of apalutamide may provide additive benefit compared to immune checkpoint blockade alone.

2 Study Objectives

2.1 Hypothesis

We hypothesize that the combination of apalutamide plus cetrelimab will achieve a clinically significant composite response rate with sufficient durability of response in mCRPC patients with evidence of treatment-emergent small cell neuroendocrine prostate cancer.

2.2 Primary Objective and Endpoints

Primary Objective	Endpoints	Time Frame
To determine the composite response rate (achieving one or more of the endpoints) of apalutamide plus cetrelimab.	• PSA50 (decline from baseline in serum PSA of ≥ 50%, confirmed by repeat measurement ≥ 4 weeks later)* AND/OR • Objective response by RECIST 1.1 criteria**	From initiation of study treatment until discontinuation of treatment (maximum of 2 years).

* to be considered evaluable for PSA50 response, patients must have baseline PSA level > 2 ng/mL

** to be considered evaluable for objective response, patients must have measurable soft tissue disease by RECIST 1.1 criteria on baseline scan assessment

2.3 Secondary Objectives and Endpoints

Secondary Objective	Endpoints	Time Frame
1. To determine safety of the combination of apalutamide and cetrelimab	• Proportion of participants with treatment-related AEs, as graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 5.0)	From initiation of study treatment until treatment discontinuation.
2. To determine the median radiographic progression-free survival by PCWG3 criteria	• Median progression free survival by PCWG3 criteria.	From initiation of study treatment until radiographic progression by PCWG3 criteria or death, whichever occurs first.
3. To determine the PSA50 and PSA90 response proportion.	• ≥ 50% and ≥ 90% decline from baseline in PSA, respectively, confirmed by repeat measurement ≥ 4 weeks after first time point*	From initiation of study treatment until maximal decline in serum PSA during study treatment.
4. To determine the median PSA progression-free survival.	• Median PSA progression-free survival by PCWG3 criteria.	From initiation of study treatment until PSA progression by PCWG3 criteria or death, whichever occurs first.
5. To determine the median overall survival.	• Median overall survival from date of start of protocol treatment until death from any cause.	From initiation of study treatment until death from any cause. (3 years)
6. To determine the objective response rate by RECIST 1.1 criteria	• Objective response rate by RECIST 1.1 criteria. • Median duration of response	From initiation of study treatment until maximal percent decline from baseline in SLD of target lesions.

* To be considered evaluable for this endpoint, patients must have baseline PSA level > 2 ng/mL.

2.4 Exploratory (Correlative) Objectives

Exploratory Objectives	Endpoints
1. To explore the association between baseline metastatic tumor characteristics including t-SCNC, AR, RB1 loss, and immune response transcriptional signatures with clinical outcomes.	Association of specific gene and transcriptional gene signatures using RNA-seq and targeted next-gen DNA sequencing with composite response rate and PFS.
2. To evaluate objective response rate and median progression-free survival by irRECIST criteria.	Objective response rate and median PFS by irRECIST.
3. To evaluate the association between immune related adverse events (irAEs) and clinical efficacy outcomes.	Association between irAEs with efficacy endpoints including composite response rate, PSA50 response, and progression-free survival.
4. To evaluate the association between baseline and change from baseline in circulating T cell and myeloid cell subsets with clinical outcomes.	Association between baseline and fold change in circulating T cell and myeloid subsets by CyTOF with efficacy endpoints including composite response, PSA50 response, and progression-free survival.
5. To explore the mechanism of skin rash in patients receiving combination of apalutamide plus cetrelimab.	Infiltration of immune cells in skin biopsies performed in patients experiencing rash on study.
6. To explore the association between genomic and epigenomic features of circulating tumor DNA with clinical outcomes.	Association between genomic and epigenomic alterations in ctDNA with clinical outcomes.
7. To explore the association between circulating tumor cell (CTC) characteristics including heterogeneity, overall CTC count, and expression of markers of interest (AR, CD56, cytokeratin) with clinical outcomes.	Association between CTC characteristics with clinical outcomes.

3 Study Design

3.1 Characteristics

This is a phase 2, single arm, Simon's two-stage evaluation of the combination of apalutamide plus cetrelimab in patients with mCRPC and histologic and/or genomic evidence of treatment-emergent small cell neuroendocrine prostate cancer who have previously progressed on at least one prior androgen signaling inhibitor. The primary study endpoint is composite response rate as defined by PSA50 response and/or objective response by RECIST 1.1 criteria.

A planned interim safety and efficacy analysis is planned after 14 patients are treated (see Section 8).

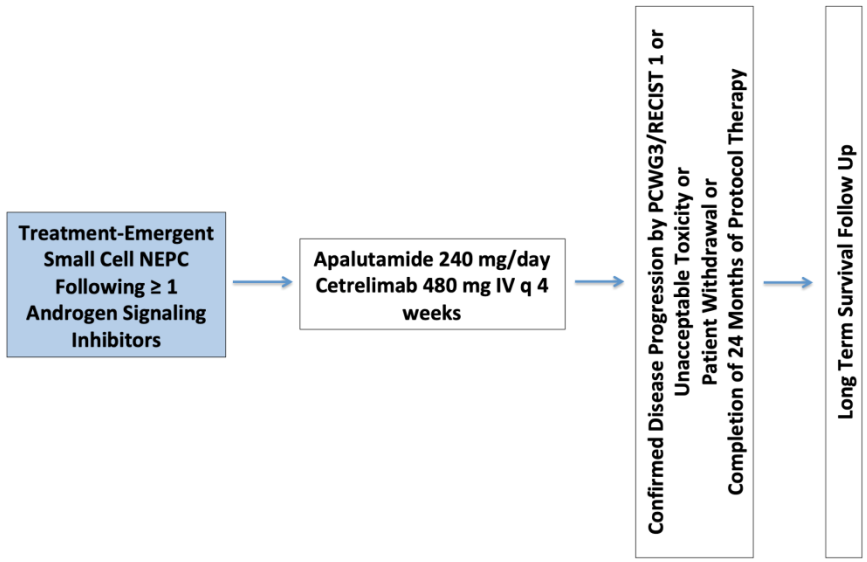

Figure 3.1 Study Schema

3.2 Sample Size

A total of 24 patients will be enrolled over an accrual period of approximately 18 months.

3.3 Eligibility Criteria

Patients must have screening procedures performed prior to Cycle 1, Day 1 of treatment and must meet all inclusion and exclusion criteria. In addition, the patient must be thoroughly informed about all aspects of the study, including study visit schedule, required evaluations, and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to enrollment. The following criteria apply to all patients enrolled onto the study unless otherwise specified.

3.3.1 Inclusion Criteria

1. Participants must have histologically confirmed prostate adenocarcinoma at the time of diagnosis, with subsequent development of metastatic castration-resistant prostate cancer. Prostate adenocarcinoma with neuroendocrine features (e.g. positive chromogranin and/or synaptophysin expression by IHC) is allowed.

2. Evidence of disease progression (PD) by PSA and/or radiographic progression by PCWG3 criteria at the time of study entry.

3. Prior progression on at least one androgen signaling inhibitor (e.g. abiraterone acetate, apalutamide, enzalutamide, darolutamide). Treatment with prior androgen signaling inhibitor may have been initiated in either the CSPC and/or CRPC setting.

4. Patients must be evaluable for the primary endpoint of composite response and must have either serum PSA > 2 ng/mL during Screening and/or measurable disease by RECIST 1.1 criteria.

5. Participants must have clinicogenomic evidence of treatment emergent small cell neuroendocrine prostate cancer as defined by one or more of the following:

    i. Histologic evidence of small cell neuroendocrine prostate cancer on evaluation of CRPC tissue by centralized pathology review

    and/or

    ii. Presence of loss-of-function mutation or deletion of *RB1* on a CLIA-approved genomic-sequencing platform. Either monoallelic or biallelic mutations in *RB1* are allowed.

6. No more than one prior line of taxane-based chemotherapy administered in the mCRPC setting. Chemotherapy administered in the castration-sensitive setting does not count towards this limit. Prior carboplatin is allowed and does not count as an additional line of therapy when given in conjunction with taxane.

7. Castrate level of serum testosterone at study entry (<50 ng/dL). Patients without prior bilateral orchiectomy are required to remain on LHRH analogue treatment for duration of study.

8. No other systemic anti-cancer therapies administered other than LHRH analogue within 14 days or, 5 half-lives, whichever is shorter, prior to initiation of study treatment. AEs related to prior anti-cancer treatment must have recovered to Grade ≤ 1 with the exception of any grade alopecia and Grade ≤ 2 neuropathy.

    b. Patients receiving apalutamide prior to study entry may continue treatment at their current apalutamide dose level without requirement for wash-out period.

9. Age ≥ 18 years

10. ECOG performance status ≤ 1 (Karnofsky performance status ≥ 70%, see Appendix 1)

11. Demonstrates adequate organ function as defined below:

<u>Adequate bone marrow function:</u>	
Absolute neutrophil count	≥ 1,500/mcL
Platelets	≥ 100,000/mcL
Hemoglobin	≥ 9.0 g/dL
<u>Adequate hepatic function:</u>	
Total bilirubin	≤ 1.5 x institutional upper limit of normal, unless elevated due to Gilbert's syndrome and direct bilirubin is within normal limits
AST (SGOT)	≤3 X institutional upper limit of normal (≤ 5 x ULN in presence of liver metastases)
ALT (SGPT)	≤3 X institutional upper limit of normal (≤ 5 x ULN in presence of liver metastases)
<u>Adequate renal function:</u>	
Serum creatinine	≤ 1.5 x institutional upper limit of normal

OR	
Calculated creatinine clearance	GFR ≥ 30 mL/min/1.73 m^2, calculated using the CKD-EPI equation

12. Ability to understand a written informed consent document, and the willingness to sign it.

13. Patients must agree to use adequate contraception and to not donate sperm prior to the study, for the duration of study participation, and 5 months after last administration of study treatment. Adequate contraception includes (see Appendix 3 for more detail):

    c. Patients who are sexually active should consider their female partner to be of childbearing potential if she has experienced menarche and is not postmenopausal (defined as amenorrhea > 24 consecutive months) or has not undergone successful surgical sterilization.

    d. Even participants who have undergone vasectomy should still use acceptable method of contraception.

    e. Acceptable methods of contraception include hormonal combined (estrogen + progesterone) or progesterone only given orally, injected or implanted; IUD, IUS, tubal ligation, vasectomy and complete sexual abstinence.

14. Patients must be willing to undergo metastatic tumor biopsy during Screening if no biopsy has previously been done. If no metastatic lesion is safely accessible to tumor biopsy, this requirement will be waived. Bone or soft tissue lesion is allowed, but soft tissue will be prioritized. If a patient has archival tissue obtained within 90 days of C1D1 the requirement for fresh tumor biopsy will be waived.

3.3.2 Exclusion Criteria

1. *De novo* small cell carcinoma of the prostate.

2. Has participated in a study of an investigational product and received study treatment or used an investigational device other than those specified in the protocol within 2 weeks of C1D1.

3. Hypersensitivity to cetrelimab, apalutamide, or any of its excipients.

4. Has received prior radiotherapy within 2 weeks of C1D1. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-central nervous system (CNS) disease.

5. Receipt of prior cetrelimab or another immune checkpoint inhibitor targeting PD-1/PD-L1 and/or CTLA-4 (e.g. pembrolizumab, nivolumab, ipilimumab). Prior treatment with sipuleucel-T is allowed.

6. Has an active autoimmune disease that has required systemic treatment in the past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Patients on low dose oral weekly methotrexate are allowed. Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) or treatment with drugs (e.g. methimazole, neomercazol, carbamazole, etc.) that function to decrease the generation of thyroid hormone by a hyper-functioning thyroid gland (e.g., in Graves' disease) is not considered a form of systemic treatment of an autoimmune disease.

7. Has received a live vaccine within 30 days prior to the first dose of study drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed. COVID-19 vaccine is allowed.

8. Individuals with concurrent second malignancy requiring active treatment at study entry that could affect safety or efficacy endpoints. Non-melanoma skin cancer, non-muscle invasive bladder cancer, and other carcinomas-in-situ are allowable exceptions.

9. Cardiac condition as defined as one or more of the following:

    a. Uncontrolled supraventricular arrhythmia or ventricular arrhythmia requiring treatment

    b. NYHA congestive heart failure class III or IV

    c. History of unstable angina, myocardial infarction, or cerebrovascular accident within 6 months prior to C1D1

    d. Uncontrolled hypertension defined as SBP ≥ 160 mm Hg and/or DBP ≥ 100 mm Hg. Treatment and re-screening are permitted.

10. History of seizure or pre-disposing condition (e.g. brain metastases). Medications known to lower seizure threshold must be discontinued at least 4 weeks prior to C1D1.

11. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy at a prednisone equivalent dose of > 10 mg daily or other form of immunosuppressive therapy within 7 days prior to first dose of study drug.

12. Human immunodeficiency virus (HIV)-infected individuals on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial (screening not required in the absence of risk factors).

13. For participants with evidence of chronic hepatitis B virus (HBV) infection (positive HBsAg and/or HBcAb), the HBV viral load must be undetectable at the time of study enrollment (screening not required in the absence of risk factors).

14. Chronic active HCV infection defined as positive viral load (screening not required in the absence of risk factors).

15. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.

16. Gastrointestinal disorder affecting absorption.

17. Has an active infection requiring intravenous (IV) antibiotics within 7 days prior to C1D1.

18. Use of a prohibited concomitant medication (see Appendix 4 and Section 6.5.1) within 7 days of C1D1. Medications known to lower seizure threshold must be discontinued at least 4 weeks prior to C1D1.

19. Major surgery within 28 days prior to C1D1. Minor procedures including biopsies, dental surgery, cataract surgery, or outpatient procedure are allowed.

20. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

21. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

3.4 Inclusion of Women and Minorities

3.4.1 Eligibility of Women and Minorities

Individuals of any race or ethnicity are eligible for this study. The inclusion of women is not appropriate for the trial design given this is a study of prostate cancer.

3.4.2 Recruitment of Minority Groups

The study recruitment strategy aims to achieve representation of minority groups that reflects the demographics of the affected population in the catchment area. In particular, this will include utilization of collaboration with Lazarex Foundation to help defray travel costs associated with clinical trial participation for patients with limited financial resources, utilization of a Redcap clinical trial tracker (ucsftrials.com), with outreach to community oncologists serving minority groups within the UCSF catchment region, engagement with the Office of Community Outreach and Engagement (COE) with the UCSF Cancer Center.

3.5 Criteria for Treatment Discontinuation

In the absence of treatment delays due to AEs, treatment (both study drugs) may continue until first occurrence of one or more of the following:

- Radiographic PD by PCWG3/RECIST 1.1 criteria. If patients are clinically stable in the judgment of treating investigator, continuation of protocol therapy is allowed until progression is confirmed by repeat tumor assessment performed ≥ 4 weeks following first scan demonstrating progression.
- Unequivocal clinical progression
- Inter-current illness that prevents further administration of treatment;
- Unacceptable AE(s);
- Participant decides to withdraw from the study;
- Significant participant non-compliance with protocol;
- Receipt of non-protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the investigator
- Study closure
- Completion of 2 years of protocol therapy.

Patients with PSA-only progression in the absence of radiographic or unequivocal progression should remain on study treatment per PCWG3 guidelines.

3.6 Criteria for Study Discontinuation

Participants will have safety follow up assessment 30 (+/- 7 days) and 100 days (+/- 14 days) following End of Treatment.

Following completion of safety follow up visits, patients will subsequently be followed for overall survival every 90 days (+/- 30 days) until death, withdrawal of consent, or the end of the study, whichever occurs first.

3.7 Primary Completion

The estimated primary completion is approximately 24 months after the study opens to accrual.

3.8 Study Completion

The expected study completion date is approximately 78 months after the study opens to accrual.

4 Investigational Products

4.1 Description, Supply and Storage of Investigational Products

4.1.1 Apalutamide

Classification

Apalutamide is in a class of medications called androgen receptor inhibitors.

Mechanism of Action

The mechanism of action of apalutamide is through inhibition of the androgen receptor. Apalutamide prevents AR nuclear translocation and DNA binding to AREs.

Unlike bicalutamide, apalutamide shows no significant agonist properties in a model of CRPC (e.g., AR-over-expressing prostate cancer cells; LNCaP/AR cells). Gene transcription of PSA and TMPRSS2 is inhibited by apalutamide and results in concentration-dependent reduction of these protein levels in vitro. Apalutamide was also shown to reduce proliferation of CRPC cells as well as increase apoptosis in mouse models of prostate cancer. In addition, apalutamide has significant anti-tumor activity in murine tumor CRPC models, where apalutamide showed dose-dependent tumor growth inhibition and tumor regression over a dose range of 0.1 to 10 mg/kg/day, with effects that were superior to bicalutamide.

Metabolism

Apalutamide is primarily metabolized by CYP2C8 and CYP3A4 to form active metabolite, N-desmethyl apalutamide. The contribution of CYP2C8 and CYP3A4 in the metabolism of apalutamide is estimated to be 58% and 13% following single dose but changes to 40% and 37%, respectively at steady state. Apalutamide represented 45% and N-desmethyl apalutamide represented 44% of the total AUC following a single oral administration of radiolabeled apalutamide 240 mg.

Contraindications

Apalutamide can cause fetal harm and potential loss of pregnancy.

Apalutamide is contraindicated for use in pregnant women because the drug can cause fetal harm and potential loss of pregnancy. Apalutamide is not indicated for use in females, so animal embryo-fetal developmental toxicology studies were not conducted with apalutamide. There are no human data on the use of apalutamide in pregnant women. Based on its mechanism of action, apalutamide may cause fetal harm when administered during pregnancy.

Formulation, Appearance, Packaging, and Labeling

Apalutamide is supplied as 60 mg tablets for oral administration. The 60-mg tablets consist of apalutamide drug substance, which is a white to slightly yellow powder. Apalutamide tablets (60 mg) are packaged in 120-count, 160 cc HDPE bottles with CRC and include desiccant, and should at all times be kept in the original packaging.

Availability

Apalutamide is being obtained as study supply provided by Janssen.

Storage and Handling

Detailed information on handling and storage conditions will accompany the clinical drug supplies to the clinical study site(s). The storage conditions and expiry will be indicated on the label of the drug product.

Side Effects

Complete and updated adverse event information is available in the Investigational Drug Brochure (IB) and/or product package insert.

Dosage and Administration

Apalutamide is administered orally on a continuous once daily dosing schedule. Each cycle of drug administration consists of 28 days. Doses from 30 to 480 mg daily were tested in the Phase 1 portion of the first clinical study (Study ARN-509-001). The therapeutic dose is 240 mg (4 x 60 mg tablets) once daily. Apalutamide can be taken with or without food.

For patients who have difficulty swallowing tablets whole, the recommended dose of apalutamide tablets may be mixed with 4 ounces (120 mL) of applesauce. Do not crush the tablets. Stir applesauce upon introduction of whole tablets as well as at 15 minutes and 30 minutes afterwards until tablets are dispersed (well mixed with no chunks remaining). Using a spoon, swallow the mixture right away. Rinse the mixture container with 2 ounces of water and immediately drink the contents. Repeat the rinse with 2 ounces of water one more time to ensure the whole dose is taken. The mixture should be consumed within one hour of preparation.

4.1.2 Cetrelimab

Classification

Antineoplastics; immunotherapies; monoclonal antibodies

Cetrelimab is a fully human IgG4 kappa mAb against PD-1 with an S228P stabilizing mutation in the hinge region.2 Cetrelimab is produced in a Chinese hamster ovary cell line.

Mechanism of Action

Antibody-dependent cell cytotoxicity; programmed cell death-1 receptor antagonists; T lymphocyte stimulants

Formulation, Appearance, Packaging, and Labeling

The drug product (DP) is supplied as a lyophilized DP that, upon reconstitution, results in a liquid for IV infusion.

Availability

Cetrelimab is being obtained as study supply provided by Janssen.

Storage and Handling

Drug product should be stored at 2°C to 8°C and protected from light.

Side Effects

Complete and updated adverse event information is available in the Investigational Drug Brochure (IB) and/or product package insert.

Physical and Chemical Characteristics

Cetrelimab has a molecular weight of approximately 148,000 Daltons and an isoelectric point of 7.2 for the major peak. The absorptivity constant for cetrelimab at 280 nm was determined to be 1.36 (mg/mL)-1cm-1.

Formulation Information

The DP has an approximate pH of 6.5 and does not contain a preservative. The fill volume is 8.6 mL prior to lyophilization. Post lyophilization and prior to use, the lyophilized DP is reconstituted with 8 mL of sterile water for injection (sWFI). The dissolution of the lyophilized cake with the sWFI yields a final concentration of 30 mg/mL. The lyophilized DP includes 7.5% overfill to allow withdrawal of up to 360 mg/vial.

The DP is filled aseptically in a glass vial. The composition of the DP is provided in Table 2.

Table 2 Composition and Concentration of Lyophilized Drug Product

Ingredient	Targeted Fill Amount per Vial[a] (mg)	Targeted Amount per mL (mg/mL)[b]
Cetrelimab	258	30
L-Histidine	9.89	1.15
L-Histidine monohydrochloride monohydrate	4.64	0.54
Sucrose	688	80
Polysorbate 20[c]	1.32	0.4[c]
EDTA, disodium salt, dihydrate crystal	0.17	0.02
Water for injection	Reconstitute with 8.0 mL	NA

a The target fill volume is 8.6 mL. This includes a 0.6 mL overfill to allow withdrawal of at least 240 mg/vial (8.0 mL volume).
b Target amount per mL post reconstitution.
c Vegetable based; low peroxide.
NA = Not applicable
EDTA = ethylenediaminetetraacetic acid

4.2 Accountability Records for Investigational Products

UCSF Investigational Drug Services (IDS) will manage drug accountability records for UCSF.

5 Treatment Plan

5.1 Dosage and Administration

Treatment will be administered on an outpatient basis.

The starting dose of apalutamide will be 240 mg daily for patients not on apalutamide prior to study enrollment. For patients on apalutamide during Screening will be permitted to continue dose prior to enrollment.

Cetrelimab will be given at the recommended phase 2 dose of 480 mg via IV on day 1 of every 28-day treatment cycle. C1D1 dose will be administered over a 60-minute infusion. In the absence of infusion-related reactions, subsequent infusions may be administered IV over 30 minutes, depending on the volume administered. Subjects should be carefully observed during cetrelimab infusions. Trained study staff at the clinic should be prepared to intervene in case of an IRR. Resources necessary for resuscitation (e.g., agents such as epinephrine and aerosolized bronchodilator, medical equipment such as oxygen tanks, tracheostomy equipment, and a defibrillator) must be available at the bedside. Attention to staffing should be considered if multiple subjects will be dosed at the same time. If an IRR develops, then the infusion should be temporarily interrupted or slowed down and the guidelines in Section 6 should be followed to manage the IRR.

For the first infusion, vital signs should be assessed before the start of the infusion, every 15 to 20 minutes during the infusion, at the end of infusion, and approximately 2 hours after the end of

infusion. After the completion of the first infusion the subject may be discharged if considered clinically stable and all other study procedures have been completed. During subsequent infusions of cetrelimab, vital signs should be assessed pre-dose, once during infusion, and at the end of infusion. Cetrelimab infusions will be prepared and administered as described in the Investigational Product Preparation Instructions (IPPI).

Table 5.1 Regimen Description

Investigational Product	Premedication; precautions	Starting Dose	Route	Schedule	Cycle Length
Cetrelimab	See below*	480 mg	IV	Day 1	28 days
Apalutamide	See below*	240 mg	Oral	Daily	

* During the first 2 cycles of study treatment, all subjects will receive prophylactic treatment with an oral H1 receptor antagonist (e.g., cetirizine, fexofenadine, loratadine) plus an H2 receptor antagonist (e.g., famotidine) plus montelukast at 10 mg daily on a continuous basis, starting at Cycle 1 Day 1. That treatment may be discontinued after Cycle 3 Day 1 at the discretion of the investigator and so long as the subject does not experience rash, pruritus, or other hypersensitivity manifestations during the first 2 cycles of treatment (see below for management of drug-related rash).

5.2 Dose Modifications and Management of Toxicity

Dose interruptions for up to 28 days are allowed. For treatment interruptions lasting > 28 days, resumption of treatment is only allowed if patients are experiencing clinical benefit and only upon approval of Principal Investigator.

If one or more agent(s) is permanently discontinued due to AE, the patient may continue to receive the other medication(s) within regimen.

5.2.1 Retreatment Criteria for Cetrelimab and Apalutamide

Table 5.2 Retreatment Criteria

Adverse Event	Requirements before each study agent administration
Absolute neutrophil count	≥ 1.0 x 10^9/L
Platelet count	≥ 50 x 10^9/L with or without platelet transfusions and/or growth factors
Hemoglobin	≥ 8.0 g/dL with or without transfusion, growth factors, or both
Fasting glucose, if prompted by HbA1c	≤ 250 mg/dL
Hyperthyroidism	Grade ≤ 2
AST and ALT	≤ 3 x ULN (≤ 5 x ULN for patients with liver metastases)
Total bilirubin	≤ 1.5 x ULN
Rash	Grade ≤ 2
Other clinically significant toxicity`	Recovery to Grade ≤ 1 or baseline

5.2.2 Dose Delay for Cetrelimab

Dose reduction of cetrelimab is not permitted. Treatment delay of cetrelimab is required until re-treatment criteria are met (Table 5.2) and for any of the following AEs:

- Grade 2 pneumonitis (recurrent Grade 2 or Grade ≥ 3 pneumonitis, cetrelimab must be permanently discontinued
- Grade 2 or 3 diarrhea or colitis
- Grade 2 nephritis with creatinine > 1.5 – 3 x ULN
- Grade 2 or 3 creatinine elevation
- Grade 2 elevation in AST or ALT except for patients with liver metastases at baseline, or total bilirubin 1.5 – 3 x ULN
- Grade 2 toxicity related to treatment with cetrelimab that is intolerable or persistent (lasts > 28 days)
- Symptomatic endocrinopathies (hypothyroidism, hyperthyroidism, hypophysitis, adrenal insufficiency diabetes)
- Grade 3 rash
- Other Grade 3 treatment related toxicity assessed as related to cetrelimab

If a cetrelimab dose must be delayed by more than 2 weeks, administration should continue at the next planned dosing date and the dose will be considered a missed dose.

Study treatment with cetrelimab should be permanently discontinued for any of the following:

- The investigator believes that for treatment-emergent toxicity it is in the best interest of the subject to discontinue study treatment
- Grade 4 toxicities except for:
    - endocrinopathies that are controlled with replacement hormones
    - Grade 4 hematologic toxicities that resolve in less than 7 days may not result in study treatment discontinuation at the discretion of the treating physician.
- Grade 2 or 3 irAEs that persist despite treatment modifications or corticosteroid dosing cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks
- A treatment-related AE does not resolve to Grade ≤1 within 12 weeks of the last dose of study drug unless otherwise agreed to by the sponsor medical monitor and the investigator based on evidence of clinical benefit
- Any non-hematological treatment-related event occurs a second time at Grade ≥3 severity
- Grade ≥3 (or recurrent Grade 2) pneumonitis
- Grade ≥3 nephritis with creatinine ≥3xULN
- Grade ≥3 elevation of AST or ALT >5xULN or total bilirubin >3xULN
    - For subjects with baseline Grade 2 elevation of AST or ALT due to liver metastasis, only Grade ≥3 elevations that are ≥50% of baseline for ≥7 days will require discontinuation of study treatment
- Grade ≥3 infusion-related reactions (IRRs)
- Immune-mediated encephalitis

Once a subject discontinues treatment, the subject may not be retreated with the study drug.

5.2.3 Dose Modification for Apalutamide

Apalutamide dose reductions due to toxicities other than rash are described in the table immediately below. Management of rash, including dose reductions, is described in Section 5.4. Apalutamide dose may be reduced as follows: first dose-level reduction to 180 mg/day, second dose-level reduction to 120 mg/day. If further dose reduction is required, apalutamide should be discontinued.

Event	Clinically Significant Hematologic and Non-Hematologic AEs Deemed Related to Apalutamide
Grade 1 or 2	Dose delay up to 4 weeks or dose reduction at the discretion of the investigator.
Grade 3	Hold apalutamide until AE has improved to Grade ≤1 or baseline and resume with a dose reduction. If apalutamide cannot be restarted within 4 weeks, it should be discontinued. Discontinue for Grade 3 toxicity that recurs after 2 dose reductions.
Grade 4	Permanently discontinue apalutamide.

Doses re-escalation back to the previous dose level may be permitted upon discretion of the Principal Investigator.

5.3 Management of Infusion-related Reactions

Guidelines for the management of IRRs are described in Table below. A reaction may manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. IRRs should be graded per NCI-CTCAE criteria.

	Management of Infusion Related Reactions
Grade 1	No intervention indicated; remain at bedside and monitor subject until recovery from symptoms, Consider diphenhydramine 50 mg (or equivalent) or paracetamol 325 to 1000 mg (acetaminophen) or both at least 30 minutes before additional study drug administration.
Grade 2	Stop infusion; start IV saline infusion; give diphenhydramine 50 mg (or equivalent) IV or paracetamol 325 to 1000 mg (acetaminophen) or both; consider corticosteroids and bronchodilator therapy. Restart infusion at 50% of initial rate: if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate; monitor subject closely. Symptoms recur: discontinue treatment at that visit; administer diphenhydramine 50 mg IV.

Grade 3-4	Stop infusion; start IV saline infusion, bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), or all 4, as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Study drug will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. In the case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine, or corticosteroids).
Secondary Prophylaxis	Prophylactic medications (after initial event): diphenhydramine 50 mg (or equivalent) or paracetamol 325 to 1000 mg (acetaminophen) or both at least 30 minutes before additional study drug administrations; if necessary, corticosteroids (recommended dose: up to 80 mg of IV methylprednisolone or equivalent) may be used.

5.4 Management of Rash

Interventions for the management of skin rash are listed in Table below. Document skin rash of any type or grade by de-identified photographs.

For skin rash with any component of desquamation, mucosal involvement, or pustules:

- Stop dosing with apalutamide and cetrelimab
- Refer to dermatologist for evaluation
- Consider skin biopsy in patients experiencing Grade ≥ 2 rash, if clinically indicated per conventional (standard of care) management.

  OPTIONAL: In the event that one or more standard of care skin biopsies are conducted, extra tissue may be collected for research (immune correlate assay to explore the mechanism of skin rah) only for patients who give optional consent for the extra tissue collection. Refer to the Lab Manual and Section 6.4.5 for additional information.

	Management of Drug Related Rash
Grade 1	• Reduce apalutamide dose by one dose level • Continue cetrelimab at current dose • Initiate oral corticosteroids. Taper corticosteroid doses as clinically indicated while monitoring clinically for worsening symptoms • Consider topical steroid cream • Reinitiate oral H1 receptor blockers, if previously discontinued • Consider re-starting H2 receptor blockers and/or montelukast, if previously discontinued • Monitor for change in severity
Grade 2 (or symptomatic grade 1[a])	• At principal investigator discretion, hold cetrelimab and apalutamide for up to 28 days and reinitiate when rash Grade is ≤1 • Reduce apalutamide dose by one dose level • Initiate oral corticosteroids or consider escalating corticosteroid dose if already prescribed. Taper corticosteroid doses as clinically indicated while monitoring clinically for worsening symptoms • Consider topical steroid cream • Reinitiate oral H1 receptor blockers, if previously discontinued • Consider re-starting H2 receptor blockers and/or montelukast, if previously discontinued • Monitor for change in severity
Grade ≥ 3[b]	• Hold cetrelimab and apalutamide for up to 28 days and reinitiate when rash • Grade is ≤1; if after 28 days, the rash has not resolved to Grade ≤1, contact the sponsor to discuss further management and possible discontinuation of study drug • Reduce apalutamide dose by one dose level at time of re-initiation • Initiate oral corticosteroids or consider escalating corticosteroid dose if already prescribed. Taper corticosteroid doses as clinically indicated while monitoring clinically for worsening symptoms • Consider topical steroid cream • Initiate oral H1 and H2 receptor blockers and montelukast, if previously discontinued • Monitor for change in severity • Consider early referral to dermatologist

a. Patient presents with other rash-related symptoms such as pruritus, stinging, or burning

b. If there is blistering or mucosal involvement, stop cetrelimab and apalutamide dosing immediately.

6 Study Procedures and Schedule of Events

The study-specific procedures and assessments are detailed in this section and outlined in the Study Calendar – Section 6.1.

Screening assessments must be performed within 28 days prior to the first dose of investigational product, unless otherwise noted. Any results falling outside of the reference ranges may be repeated at the discretion of the investigator.

All on-study visit procedures are allowed a window of ± 3 days unless otherwise noted. Treatment or visit delays for public holidays or weather conditions do not constitute a protocol violation.

6.1 Study Calendar

Period/ Procedure	Screening	Cycle 1		Cycle 2+	End of Treatment	Safety Follow-up	Safety Follow-up	Long Term Follow-Up
Study Day/Visit Day	**Day -28 to -1 unless otherwise noted**	**D1 (± 3d)**	**D15 (± 3d)**	**D1 (± 3 days)**		**30 days (± 7 days) post-last dose**	**100 days (± 14 days) post-last dose**	**Every 90 days[1] (± 30 days)**
Study Treatment/Drug Administration								
Apalutamide		X						
Cetrelimab infusion		X		X				
Administrative Procedures								
Informed Consent	X							
Clinical Assessments								
Medical History	X							
Concurrent Medications	X	X	X	X				
Physical Exam[14]	X[13]	X[13]	X[13]	X[13]	X[13]			
Vital Signs (blood pressure and heart rate)	X	X	X	X	X			
AE assessment	X	X	X	X	X	X	X[15]	
ECOG/Karnofsky Performance Status	X	X	X	X	X			
Survival/Long-term Follow-up[1]								X
Laboratory Assessments								
Hematology [2]	X	X	X	X	X	X		
Chemistry [3]	X	X	X	X	X	X		
Thyroid Function Tests [4]	X	X		X	X			
Serum PSA	X	X		X	X			
Serum Total Testosterone	X							
Whole blood peripheral immune markers[5]		X		X[5]	X			

Period/ Procedure	Screening	Cycle 1		Cycle 2+	End of Treatment	Safety Follow-up	Safety Follow-up	Long Term Follow-Up
Study Day/Visit Day	**Day -28 to -1 unless otherwise noted**	**D1 (± 3d)**	**D15 (± 3d)**	**D1 (± 3 days)**		**30 days (± 7 days) post-last dose**	**100 days (± 14 days) post-last dose**	**Every 90 days[1] (± 30 days)**
Isolation of peripheral blood mononuclear cells (PBMC)				X[10]	X[10]			
Circulating tumor cells[11]		X[11]		X[11]	X[11]			
Circulating tumor DNA[12]		X[12]		X[12]	X[12]			
Imaging Procedures								
CT Chest, Abdomen, and Pelvis[6]	X			X				
Bone scan[6]	X			X				
CT/MR brain[7]								
Tissue Collection/ Biopsy								
Tumor Tissue Collection[8]	X				X			
Skin biopsy for Grade ≥2 rash, if clinically indicated[9]		X[9]						

[1] Patients will be followed for overall survival every 90 days (+/- 30 days) from last dose of study treatment. Follow up will be conducted via chart review and/or telephone call.

[2] Including complete blood cell (CBC) with differential and platelet count. All laboratory assessments have a window of +/- 3 days.

[3] Chemistry panel includes: sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN)/creatinine, calcium, alkaline phosphatase (ALP), ALT/AST, total bilirubin. All laboratory assessments have a window of +/- 3 days.

[4] Thyroid function tests - including thyroid-stimulating hormone (TSH), with reflex free T4, total/free T3. Thyroid function tests will be performed on Day 1 of each Treatment Cycle.

[5] Whole Blood for peripheral immune marker assessment will be collected on C1D1 (pre-dose), C2D1 (pre-dose), C3D1 (pre-dose), and End of Treatment.

[6] Tumor assessment will be performed with CT Chest/Abdomen/Pelvis and whole-body bone scan during screening, C4D1 (-14d), C7D1 (-14d) and on D1 (-14d) of every 4 cycles thereafter (e.g. C11D1, C15D1). If PD by RECIST1.1/PCWG3, confirmatory scans are required ≥ 4 weeks following first scan showing progression. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

[7] CT with contrast or MR brain is required during Screening only if history of brain metastases or clinical suspicion.

[8] Optional Tumor biopsy will be performed during Screening. Biopsy only required if no biopsy has previously been done. If no metastatic lesion is safely accessible to tumor biopsy, this requirement will be waived. Bone or soft tissue lesion is allowed, but soft tissue will be prioritized. If a patient has archival tissue obtained within 90 days of C1D1, and no intervening therapy between tissue acquisition and C1D1, the requirement for fresh tumor biopsy will be waived. Tumor biopsy at progression is

optional and should be the same lesion as Screening biopsy whenever feasible. Biopsy at PD also optional. Refer to Lab Manual for detail regarding tissue collection/biopsy.

[9] If a subject experiences a treatment-emergent rash of Grade ≥ 2, consider referral to Dermatology for skin biopsy if clinically indicated per conventional (standard of care) rash management. See Section 5.4 for rash management.
OPTIONAL: In the event that one or more standard of care skin biopsies are conducted, extra tissue may be collected for research (immune correlate assay to explore the mechanism of skin rash) only for patients who give optional consent for the extra tissue collection. Refer to the Lab Manual and Section 6.4.5 for additional information.

[10] PBMCs will be isolated from blood of patients experiencing Grade ≥ 2 rash (within 14 days of symptom onset when feasible) and from patients which have not experienced any Grade rash at end of treatment.

[11] Whole blood will be collected on C1D1 (pre-dose), C2D1 (pre-dose), C3D1 (pre-dose), and End of Treatment. Samples were stored at Epic Sciences for circulating tumor cell analysis, however, as of Amendment 1.8 dated 07-24-2023, Epic Sciences is no longer analyzing these samples. All remaining samples stored at Epic Sciences will be returned to UCSF and stored at the UCSF CTSI lab. Whole blood will continue to be collected and stored at the CTSI for future research..

[12] Plasma for circulating tumor DNA analysis including 5-hydroxymethyl cytosine (5-hmC) sequencing will be collected on C1D1 (pre-dose), C2D1 (pre-dose), C3D1 (pre-dose), and End of Treatment. Plasma will be sent to the Feng laboratory at UCSF.

[13] Height at screening only. Weight at each physical exam visit (patient will self-report if PE is during a telemedicine visit).

[14] On Cycle 1 Day 15 and the End of Treatment (EOT) visit, the physical exam may be done via a telemedicine visit. Other physical exams must be performed in-person. Vital signs (BP and heart rate) will be self-reported by the patient when the physical exam is a telemedicine visit.

[15] If AE assessment done at EOT visit, just needs to be done at 30-day Safety Follow-Up

6.2 Participant Registration

A written, signed, informed consent form (ICF) and a Health Insurance Portability and Accountability Act (HIPAA) authorization must be obtained before any study-specific assessments are initiated. A copy of the signed ICF will be given to the subject and a copy will be filed in the medical record. The original will be kept on file with the study records.

All participants consented to the study will be registered in OnCore®, the UCSF Helen Diller Family Comprehensive Cancer Center Clinical Trial Management System (CTMS). The system is password protected and meets HIPAA requirements.

6.3 Schedule of Procedures and Observations

6.3.1 Pretreatment Period

6.3.1.1 Screening Assessments

The Screening procedures and assessments must be completed within 28 days of initiating study treatment.

- Clinical Assessments
  - Complete medical history
  - Concomitant medication review
  - Physical examination (including height and weight) and vital signs (BP and heart rate)
  - AE assessment
  - Performance status
- Laboratory Assessments
  - Hematology labs - CBC with differential and platelet count
  - Blood chemistry assessment, including: ALP, ALT/AST, total bilirubin, calcium, BUN, creatinine, potassium, sodium, chloride, bicarbonate
  - Thyroid function tests - including thyroid-stimulating hormone (TSH), with reflex free T4 and total/free T3
  - Serum Prostate Serum Antigen (PSA)
  - Testosterone level
- Imaging Procedures
  - CT of Chest, Abdomen and Pelvis (with IV contrast unless contra-indicated)
  - Bone scan
  - CT or MR brain with contrast (only if history of brain metastases or clinical suspicion)
- Tumor Tissue Collection (optional): A pre-treatment core biopsy is only required of patients who have not had a previous biopsy. In these cases, a biopsy must be obtained prior to study enrollment for all patients with safely accessible lesion, unless metastatic biopsy has been previously obtained within 90 days of C1D1 without intervening systemic therapy. For all other patients, the biopsy is optional.

6.3.2 Treatment Period

6.3.2.1 Study Procedures, Cycle 1, Day 1

- Study Treatment/Drug Administration
  - Initiation or continuation of apalutamide
  - Cetrelimab infusion
- Clinical Assessments
  - Concomitant medication review
  - Physical examination (including weight) and vital signs
  - AE assessment
  - Performance status
- Laboratory Assessments
  - Hematology labs - CBC with differential and platelet count
  - Blood chemistry assessment, including: ALP, ALT/AST, total bilirubin, calcium, BUN, creatinine, potassium, sodium, chloride, bicarbonate,
  - Thyroid function tests - including thyroid-stimulating hormone (TSH), free T4, total/free T3
  - Serum PSA
  - Whole blood peripheral immune markers (pre-dose)
  - Circulating tumor cells (pre-dose)
  - Circulating tumor DNA (pre-dose)

6.3.2.2 Study Procedures, Cycle 1, Day 15

- Study Treatment/Drug Administration
  - Continuation of apalutamide
- Clinical Assessments
  - Concomitant medication review
  - Physical examination (including weight), may be done via a telemedicine visit
  - Vital signs (BP and heart rate)
  - AE assessment
  - Performance status
- Laboratory Assessments
  - Hematology labs - CBC with differential and platelet count
  - Blood chemistry assessment, including: ALP, ALT/AST, total bilirubin, calcium, BUN, creatinine, potassium, sodium, chloride, bicarbonate

6.3.2.3 Study Procedures Cycle 2+, Day 1

- Study Treatment/Drug Administration
  - Continuation of apalutamide
  - Cetrelimab infusion

- Clinical Assessments
  - Concomitant medication review
  - Physical examination (including weight)
  - Vital signs (BP and heart rate)
  - AE assessment
  - Performance status
- Laboratory Assessments
  - Hematology labs - CBC with differential and platelet count
  - Blood chemistry assessment, including: ALP, ALT/AST, total bilirubin, calcium, BUN, creatinine, potassium, sodium, chloride, bicarbonate
  - Thyroid function tests - including thyroid-stimulating hormone (TSH), reflex free T4, reflex total/free T3 (D1 of every cycle)
  - Serum PSA
  - Whole blood peripheral immune markers (C2D1, C3D1, pre-dose)
  - Isolation of peripheral blood mononuclear cells (PBMC)
  - Circulating tumor cells (C2D1, C3D1, pre-dose)
  - Circulating tumor DNA (C2D1, C3D1, pre-dose)
- Imaging Procedures
  - CT of Chest, Abdomen and Pelvis (with IV contrast unless contra-indicated) and whole-body bone scan (C4D1, C7D1, and D1 of every 4 cycles thereafter). Scans have window of -14 days and may be performed earlier than pre-specified as clinically indicated.

6.3.2.4 Other On-Treatment Procedures

- Dermatology referral and tissue collection/skin biopsy:

  If a subject experiences a treatment-emergent rash of Grade ≥ 2, consider referral to Dermatology for skin biopsy if clinically indicated per conventional (standard of care) rash management. See Section 5.4 for rash management.

  OPTIONAL: In the event that one or more standard of care skin biopsies are conducted, extra tissue may be collected for research (immune correlate assay to explore the mechanism of skin rash) only for patients who give optional consent for the extra tissue collection. Refer to the Lab Manual and Section 6.4.5 for additional information.

6.3.3 End-of-Treatment Study Procedures

- Clinical Assessments
  - Physical examination (including weight), may be done via a telemedicine visit
  - Vital Signs (BP and heart rate)
  - AE assessment
  - Performance status
- Laboratory Assessments
  - Hematology labs - CBC with differential and platelet count

  - Blood chemistry assessment, including: ALP, ALT/AST, total bilirubin, calcium, BUN, creatinine, potassium, sodium, chloride, bicarbonate
  - Thyroid function tests - including thyroid-stimulating hormone (TSH), reflex free T4, reflex total/free T3
  - Serum PSA
  - Whole blood peripheral immune markers
  - Isolation of peripheral blood mononuclear cells (PBMC)
  - Circulating tumor cells
  - Circulating tumor DNA
- Tissue Collection/Biopsy (optional)
  - Tumor Tissue Collection: A CT-guided core biopsy is optional at End of Treatment. The same lesion that was biopsied during Screening should be biopsied whenever feasible.

6.3.4 30-day Safety Follow Up (+/- 7 days)

- Clinical Assessments
  - AE assessment (may be performed via telephone)
- Laboratory Assessments
  - Hematology labs - CBC with differential and platelet count
  - Blood chemistry assessment, including: ALP, ALT/AST, total bilirubin, calcium, BUN, creatinine, potassium, sodium, chloride, bicarbonate

6.3.5 100-day Safety Follow-Up (+/- 14 days)

- Clinical Assessments
  - AE assessment (may be performed via telephone; if AE assessment was done at EOT visit, 100-day Safety Follow-Up AE assessment not required)

6.3.6 Long Term/Survival Follow-up

Patients will be followed for overall survival every 90 days (+/- 30 days) from last dose of study treatment, until death, withdrawal of consent, or the end of the study, whichever occurs first.

Follow up will be conducted via chart review and/or telephone call.

End of study is defined as three years after last dose of study drug.

6.4 Correlative Studies

6.4.1 Metastatic Tumor Biopsy

Metastatic tumor biopsies are only required if the patient has no previous metastatic biopsy (within 90 days of C1D1 without intervening systemic therapy).

Metastatic tumor biopsy is at Screening is optional.

Assays to be performed include RNA-seq, targeted genomic sequencing, histological assessment, and tumor content permitting, additional IHC and/or DNA-seq.

Metastatic tumor biopsy is optional at PD.

6.4.2 Peripheral blood immune profiling

The Fong laboratory at UCSF will perform whole blood immune profiling for this study. Research blood (6 heparin green top tubes) will be collected C1D1 (pre-dose), C2D1, C3D1 (pre-dose), and EOT and transported to the Fong laboratory as per instructions in the Lab Manual.

6.4.3 Circulating tumor cells

Circulating tumor cells were analyzed using the Epic Sciences' platform. Morphology and heterogeneity, quantification of total number of CTCs, and expression of cell surface markers including AR, CD46, and CK, were analyzed. As of Protocol Amendment 1.8 dated 07-24-2023, Epic Sciences is no longer providing analysis of the samples. Blood will continue to be collected on C1D1, C2D1, C3D1, and EOT, and will be stored at the UCSF CTSI Lab. All samples stored at Epic Sciences will be returned to UCSF, and will be stored in the CTSI Lab.

6.4.4 Circulating tumor DNA

The Feng laboratory at UCSF will analyze circulating tumor DNA for genomic alterations including alterations of *RB1*, *TP53*, and *PTEN*. In addition, 5-hydroxy methyl cytosine (5-hmC) sequencing of ctDNA will be performed to infer gene expression of key genes of interest including AR, ASCL1, EZH2, RB1, PTEN, TP53, and CTNNB1. Plasma for ctDNA analyses will be collected on C1D1, C2D1, C3D1, and EOT.

6.4.5 Immune correlate assay to explore the mechanism of skin rash

If a subject experiences a treatment-emergent rash of Grade ≥ 2, consider referral to Dermatology for skin biopsy if clinically indicated per conventional (standard of care) rash management. See Section 5.4 for rash management.

OPTIONAL: In the event that one or more standard of care skin biopsies are conducted, extra tissue may be collected for research (immune correlate assay to explore the mechanism of skin rash) only for patients who give optional consent for the extra tissue collection (Refer to the Lab Manual). The risk of obtaining additional skin biopsy specimens at the time of a standard of care skin biopsy procedure will be minimized. The biopsy site and number of punches/samples obtained will be determined in consultation with the professional performing the procedure based on safe accessibility and size of lesion.

6.5 Use of Concurrent/Concomitant Medications

6.5.1 Prohibited Concomitant Medications

Participants are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial (see Appendix 4):

- Antineoplastic systemic chemotherapy or biological therapy other than LHRH analogue
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents not specified in this protocol
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary metastatic lesion or to the brain may be allowed at the investigator's discretion.

Live vaccines within 30 days prior to the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed. ***COVID-19 vaccine is allowed.***

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited during the study, discontinuation from study therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study treatment requires the mutual agreement of the Principal Investigator and subject.

Prohibited Therapies

- Aminophylline/theophylline
- Atypical antipsychotics (e.g., clozapine, olanzapine, risperidone, ziprasidone)
- Bupropion
- Lithium
- Meperidine and pethidine
- Phenothiazine antipsychotics (e.g., chlorpromazine, mesoridazine, thioridazine)
- Tricyclic and tetracyclic antidepressants (e.g., amitriptyline, desipramine, doxepin, imipramine, maprotiline, mirtazapine)
- Systemic immunotherapy or immunosuppressants (e.g., ipilimumab, cyclosporine, infliximab). However, the use of immunosuppressive medications for the management of irAEs, IRRs, or in subjects with contrast allergies is acceptable.
- Live or live attenuated vaccines; annual inactivated influenza vaccine is permitted
- Other anticancer therapies, excluding GnRH analog

6.5.2 Acceptable Concomitant Medications/Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the Investigator determines the events to be related to cetrelimab.

Note: If after the evaluation of the event, it is determined not to be related to cetrelimab, the Investigator does not need to follow the treatment guidance. Refer to guidelines regarding dose modification and supportive care.

Patients are recommended to use bone-modifying agents (e.g. denosumab, zoledronic acid) during Screening and Treatment phases of the study to decrease risk of fracture.

LHRH analogues are required during Study Treatment except for patients with history of bilateral orchiectomy.

Patients are recommended to taper off prednisone prior to study enrollment but are allowed to take doses up to ≤ 10 mg daily prednisone or prednisone equivalent. Doses of steroids higher than prednisone 10 mg daily (or prednisone equivalent) are permitted only for the treatment of immune related AEs.

Treatment with antiemetic therapy will be permitted, if clinically indicated.

Treatment with filgrastim or other colony stimulating factors will be permitted for Grade 3 or higher hematologic toxicity as per Package Insert but may not be used prophylactically.

Treatment required for care of complications/AEs arising from the cancer and/or treatment will be permitted.

6.6 Lifestyle/Dietary Restrictions

Participants should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

Apalutamide may be taken with or without food.

6.6.1 Contraception and Pregnancy

Study medications may have adverse effects on a fetus in utero. Refer to Appendix 3 for approved methods of contraception.

7 Reporting and Documentation of Results

7.1 Evaluation of Efficacy: Antitumor Effect – Solid Tumors

Response and progression in this study will be evaluated using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009] with use of PCWG3 criteria for assessment of new/pre-existing bone lesions. 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 RECIST v1.1 criteria.

7.1.1 Definitions

Evaluable for toxicity

All participants will be evaluable for toxicity from the time of their first protocol-defined treatment on C1D1.

Evaluable for objective 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 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.

7.1.2 Disease Parameters

Measurable disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area considered measurable only if radiographic evidence of progression following completion of prior radiation treatment.

Malignant lymph nodes

To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease (Tumor Markers)

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm [<1 cm] or pathological lymph nodes with ≥10 to <15 mm [≥1 to <1.5 cm] short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, 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 organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. 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 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.

Non-target lesions

All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. 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"). Bone lesions may be measurable if ≥ 1 cm on MRI. Measurements of these lesions are not required, but the presence or absence of each will be noted throughout follow-up.

Non-measurable disease (Tumor Markers)

Non-measurable disease is all other lesions (or sites of disease), including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm using spiral CT scan). Leptomeningeal disease, ascites, pleural or pericardial effusion, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques are all non-measurable.

7.1.3 Methods for Evaluation of Measurable Disease

All measurements will be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations will be performed as closely as possible to the beginning of treatment and never more than 30 days before the beginning of the treatment.

The same method of assessment and the same technique will be used to characterize each identified and reported lesion at baseline and during follow-up whenever feasible. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm (≥1 cm) 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 slice thickness is 5 mm (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), the minimum size for 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.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic

quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Tumor markers: Serum PSA will be used as part of the composite response definition as outlined in Section 2 and Section 8 of the protocol.

7.1.4 Response Criteria

Evaluation of Target Lesions

Complete Response (CR)

Disappearance of all target lesions, determined by two separate observations conducted not less than 4 weeks apart. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (the sum may not be "0" if there are target nodes). There can be no appearance of new lesions.

Partial Response (PR)

At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. There can be no appearance of new lesions.

Progressive Disease (PD)

At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (0.5 cm). (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD)

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

Evaluation of Non-Target Lesions

Complete Response (CR)

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

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

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.

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 participant's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Table 7.1 Response Criteria For Participants with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as PD.
Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of PD at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

Table 7.2 Response Criteria for Participants with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

Duration of Response

Duration of overall response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

Evaluation of non-measurable bone disease per PCWG3 criteria

Bone scans obtained after the baseline evaluation will be used to evaluate post-treatment changes. Bone scans obtained will be evaluated as either “no new lesions” or “new lesions” on the tumor measurement forms.

- For the first scheduled reassessment: If 2 or more new bone lesions are detected at the first scheduled evaluation (9 weeks), confirmatory bone scan is required 6 or more weeks later. If < 2 additional new lesions are observed on the confirmatory bone scan, study therapy is continued. If ≥ 2 additional new lesions are observed, then the patient has experienced radiographic progression by PCWG criteria. Progression in this situation is dated as the time of the first reassessment scan.
- For subsequent scheduled reassessments: If no new lesions are observed, study therapy will continue. If ≥ 2 new bone lesions are observed, this is evidence of radiographic PD. Date of progression is the date at which the first scan demonstrating radiographic progression was obtained.

Evaluation of Post-treatment PSA changes

All patients will be evaluated for PSA decline. Patients with disease that is not measurable will be eligible for this study and will be assessed for response based on changes in PSA and serial bone scans (if appropriate). The baseline serum PSA must be at least 2 ng/mL to be evaluable for PSA response.

- 50% and 90% PSA Decline: PSA decline of at least 50% and 90%, respectively, from baseline confirmed by a second measurement at least 3 weeks later. The reference for these declines should be a PSA measured within 2 weeks prior to starting therapy.
- PSA Progression: Prostate Cancer Working Group 3 (PCWG3) Criteria will be reported. PSA progression occurs when the PSA has increased 25% or greater above nadir and an absolute increase of 2 ng/mL or more from the nadir is documented. Where no decline is observed, PSA progression similarly occurs when a 25% increase from baseline value along with an increase in absolute value of 2 ng/mL or more. PSA progression (without evidence of progression on scans) will not be criteria for discontinuation of study therapy.
- PSA Response Duration: The PSA response duration commences on the date of the first 50% decline in PSA. The response duration ends when the PSA value increases by 25% above the nadir, provided that the increase in the absolute-value PSA level is at least 5 ng/mL or back to baseline, whichever is lower
- Progressive disease by PSA is defined by PSA progression, noted above.

- Time to PSA Progression: The start of the time to PSA progression is the day treatment is initiated. The end date is the date of the first PSA rise over the determined PSA PD value.

Definition of Progressive Disease

A composite definition of PD will be defined by first occurrence of any one of the following:

- Appearance of new metastatic lesions outside the bone
- New metastatic lesions on bone scan confirmed as described above
- Development of an indication for radiotherapy while on treatment
- Unequivocal progression of non-target lesions
- Global deterioration of health status requiring discontinuation of treatment without objective evidence of PD
- Development of an indication for non-protocol systemic therapy

Patients experiencing radiographic progression in the absence of clinical progression are allowed to remain on treatment until follow up scan confirms progression.

Note that PSA progression (as defined above) alone does not meet the criteria for progressive disease.

7.2 Evaluation of Safety

The safety parameters for this study include all clinically significant laboratory abnormalities, clinically significant physical findings, clinically significant findings on scans and/or ECG, and spontaneous reports of AEs reported to the investigator by participants.

Toxicity will be assessed according to the NCI CTCAE version 5.0. Safety analyses will be performed for all participants from the time of first study drug administration on C1D1.

7.3 Definitions of Adverse Events

7.3.1 Adverse Event

An AE (also known as an adverse experience) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. More specifically, an AE (can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An AE can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

7.3.2 Adverse Reaction

An adverse reaction is defined as any AE caused by the use of a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

7.3.3 Suspected Adverse Reaction

A suspected adverse reaction is defined as any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of IND safety reporting, “reasonable possibility” indicates that there is evidence to suggest a causal relationship between the drug and the AE.

A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

7.3.3.1 Unexpected

An AE or suspected adverse reaction is considered unexpected if it is not listed in the investigator brochure or package insert(s), or is not listed at the specificity or severity that has been observed, or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

"Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

AEs that would be anticipated to occur as part of the disease process are considered unexpected for the purposes of reporting because they would not be listed in the investigator brochure. For example, a certain number of non-acute deaths in a cancer trial would be anticipated as an outcome of the underlying disease, but such deaths would generally not be listed as a suspected adverse reaction in the investigator brochure.

Some AEs are listed in the Investigator Brochure as occurring with the same class of drugs, or as anticipated from the pharmacological properties of the drug, even though they have not been observed with the drug under investigation. Such events would be considered unexpected until they have been observed with the drug under investigation. For example, although angioedema is anticipated to occur in some participants exposed to drugs in the angiotensin-converting enzyme inhibitor class and angioedema would be described in the investigator brochure as a class effect, the first case of angioedema observed with the drug under investigation should be considered unexpected for reporting purposes.

For apalutamide, the link to the package insert is:

http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/ERLEADA-pi.pdf

For cetrelimab, the expectedness of an AE will be determined by whether or not it is listed in the Investigator's Brochure.

7.3.3.2 Serious

An AE or suspected adverse reaction is considered serious if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- Life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life function
- Congenital anomaly/birth defect

Important medical events that may not result in death, are life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent

one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

7.3.3.3 Life-threatening

An AE or suspected adverse reaction is considered life-threatening if, in the view of either the investigator or sponsor, its occurrence places the participant at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

7.3.3.4 Adverse Events of Special Interest

AEs of special interest are events that the drug manufacturer is actively monitoring as a result of a previously identified signal (even if non-serious).

For cetrelimab, the AEs of special interest are:

- Immune-related reactions

There are no non-serious AEs of special interest for apalutamide.

Any AE of special interest that is to be reported to the drug manufacturer should be recorded on a Serious Adverse Event Report Form and be reported to the drug manufacturer **within 24 hours of becoming aware of the event.**

7.3.3.5 Product Quality Complaint (PQC)

A product quality compliant is defined as any suspicion of a product defect related to a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product, or delivery system. Not all PQCs involve a subject. Lot and batch numbers are of high significance and need to be collected whenever available.

Examples of PQC include but not limited to:

- Functional Problem: e.g., altered delivery rate in a controlled release product
- Physical Defect: e.g. abnormal odor, broken or crushed tablets/capsules
- Potential Dosing Device Malfunction: e.g., autoinjector button not working, needle detaching from syringe
- Suspected Contamination
- Suspected Counterfeit

7.3.3.6 Special Reporting Situations

Safety events of interest for a J&J medicinal product that require expediting reporting and/or safety evaluation include, but are not limited to:

- Drug exposure during pregnancy (maternal and paternal)
- Overdose of a J&J medicinal product
- Exposure to a J&J medicinal product from breastfeeding
- Suspected abuse/misuse of a J&J medicinal product

- Inadvertent or accidental exposure to a J&J medicinal product
- Medication error involving a J&J medicinal product (with or without patient exposure to the J&J medicinal product, e.g., name confusion)
- Suspected transmission of any infectious agent via administration of a medicinal product

Special situations should be recorded on the Adverse Event page of the CRF.

Any special situation that meets the criteria of a serious adverse event should be recorded on a MedWatch form and be reported to the J&J **within 24 hours of becoming aware of the event.**

7.3.3.7 Pregnancy

Because the J&J medicinal product may have an effect on sperm, pregnancies in partners of male subjects exposed to a J&J medicinal product will be reported by the PRINCIPAL INVESTIGATOR **within 24 hours of their knowledge of the event** using the Serious Adverse Event Form. Depending on local legislation this may require prior consent of the partner.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

7.3.4 Recording of Adverse Events

Refer to the Data Safety Monitoring Plan, located in Appendix 2.

7.3.5 Follow-up of Adverse Events

All participants who experience AEs will be followed with appropriate medical management until resolved or stabilized, as determined by the investigator, or until the initiation of new anti-cancer therapy, whichever occurs first. For selected AEs for which administration of the investigational product was stopped, a re-challenge of the subject with the investigational drug may be conducted if considered both safe and ethical by the investigator.

7.3.6 Adverse Events Monitoring

Refer to the Data Safety Monitoring Plan, located in Appendix 2.

7.3.7 Expedited Reporting

Reporting to the Data and Safety Monitoring Committee

If a death occurs during the treatment phase of the study or within 100 days after the last administration of the study drug(s) and it is determined to be related either to the study drug(s) or to a study procedure, the Investigator or his/her designee must notify the DSMC Chair (or qualified alternate) within 1 business day of knowledge of the event. The contact may be by phone or e-mail.

Reporting to Institutional Review Board

The UCSF PI must report events to the UCSF IRB according to institutional guidelines.

UCSF IRB website for guidance in reporting AEs: https://irb.ucsf.edu/adverse-event

The PI at each participating site is responsible for reporting events to the IRB of record according to IRB guidelines.

Expedited Reporting to the FDA

If the study is being conducted under an IND, the Sponsor (or the Sponsor-Investigator) is responsible for determining whether or not the suspected adverse reaction meets the criteria for expedited reporting in accordance with federal regulations (21 CFR §312.32).

The Sponsor (or Sponsor-Investigator) must report in an IND safety report any suspected adverse reaction that is both serious and unexpected. The Sponsor needs to ensure that the event meets all three definitions:

- Suspected adverse reaction
- Unexpected
- Serious

If the AE does not meet all three of the definitions, it should not be submitted as an expedited IND safety report.

The timeline for submitting an IND safety report to FDA is no later than **15 calendar days** after the Investigator determines that the suspected adverse reaction qualifies for reporting (21 CFR 312.32(c)(1)).

Any unexpected fatal or life-threatening suspected adverse reaction will be reported to FDA no later than **7 calendar days** after the Investigator's initial receipt of the information (21 CFR 312.32(c)(2)).

Any relevant additional information that pertains to a previously submitted IND safety report will be submitted to FDA as a Follow-up IND Safety Report without delay, as soon as the information is available (21 CFR 312.32(d)(2)).

Reporting to Industry Partners

All AEs and special situations, whether serious or non-serious, related or not related, following exposure to [redacted] medicinal product are to be documented by the investigator and recorded in the CRF and in the subject's source records. Investigators must record in the CRF (if consistent with Sponsor policies) or MedWatch form their opinion concerning the relationship of the AE to a [redacted] medicinal product.

All (serious and non-serious) AEs reported for a [redacted] medicinal product should be followed-up in accordance with clinical practice.

SAEs, Adverse Events of Special Interest and Special Reporting Situations

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

The Sponsor and the Investigator) will transmit all SAEs, AEs of Special Interest and special situations following exposure to a [redacted] product under study using MedWatch Form 3500A in accordance with Section 9 of this Exhibit B, Transmission Methods, in English **within twenty-four (24) hours of becoming aware of the event(s).**

All follow-up information for serious adverse events that are not resolved at the end of the study or by the time of patient withdrawal must be reported directly by the PRINCIPAL INVESTIGATOR, **within 24 hours becoming aware**, [redacted] using the Serious Adverse Event Report

All available clinical information relevant to the evaluation of a related SAE, AEs of Special Interest, serious ADR or special situation is required.

- The INSTITUTION and/or PRINCIPAL INVESTIGATOR is responsible for ensuring that these cases are complete and if not are promptly followed-up. A safety report is not considered complete until all clinical details needed to interpret the case are received. Reporting of follow-up information should follow the same timeline as initial reports.
- Copies of any and all relevant extraordinary (not including routine initial or follow-up ICSR submission) correspondences with regulatory authorities and ethics committees regarding any and all serious adverse irrespective of association with the J&J Product under study, are to be provided to the COMPANY using a transmission method in Section 9 within **24 hours of such report or correspondence being sent to applicable health authorities.**

Non-Serious AEs

All non-serious AEs should be reported to COMPANY according to the timeframe outlined in the Agreement section entitled Reporting of Data.

PQC Reporting

A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of patients, investigators, and the COMPANY, and are mandated by regulatory agencies worldwide. The COMPANY has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information. Lot and/or Batch #s shall be collected or any reports failure of expected pharmacological action (i.e., lack of effect). The product should be quarantined immediately and if possible, take a picture.

All initial PQCs involving a J&J medicinal product under study must be reported to the COMPANY by the PRINCIPAL INVESTIGATOR **within 24 hours after being made aware of the event**. The J&J contact will provide additional information/form to be completed.

If the defect for a [redacted] medicinal product under study is combined with either a serious adverse event or non-serious AE, the PRINCIPAL INVESTIGATOR must report the PQC to the COMPANY according to the serious adverse event reporting timelines. A sample of the suspected product should be maintained for further investigation if requested by the COMPANY.

8 Statistical Considerations and Evaluation of Results

8.1 Sample Size Considerations

8.1.1 Sample Size and Power Estimate

The sample size determination is based on the primary endpoint of the study, the composite response rate. Composite response rate is defined in Section 3 and below in Section 8.3.2.

Based on historical control data, the null hypothesis is a 15% composite response rate. Simon's two-stage minimax design will be used. The null hypothesis that the true response rate is 15% will be tested against a one-sided alternative. In the first stage, 14 patients will be accrued. If there are 2 or fewer composite responses in these 14 patients, the study will be stopped. Otherwise, 10 additional patients will be accrued for a total of 24 patients. The null hypothesis will be rejected if 8 or more responses are observed in 24 patients. This design yields a type I error rate of 0.025 and power of 80.2% when the true composite response rate is 40%.

8.1.2 Accrual Estimates

Based on our historical data, we estimate that approximately 15% of all mCRPC patients will meet the definition of treatment-emergent small cell NEPC (t-SCNC) as outlined in the Eligibility criteria in Section 3 of the protocol. We estimate an accrual rate of approximately 1.5 patients per month, and estimated accrual duration of approximately 18 months.

8.2 Interim Analyses and Stopping Rules

An interim analysis for safety and efficacy will be conducted after 14 patients are enrolled and have completed treatment. Criteria for efficacy stopping rule are outlined above in Section 8.1.1. With respect to interim safety analysis, if more than 33% (5 or more patients) experiences a Grade ≥ 3 treatment-related AE in cycle 1, excluding anemia or clinically insignificant laboratory abnormality, study accrual will be halted and alternative dose level and/or schedule may be investigated following safety analysis and protocol amendment.

8.3 Analyses Plans

8.3.1 Analysis Population

The safety population is defined as any patients who received at least one dose of protocol therapy on study.

The analysis population for the primary composite response endpoint includes all patients evaluable for composite response, defined as possessing either a Screening PSA > 2 ng/mL and/or measurable disease by RECIST 1.1 criteria.

The analysis population for the time-to-event efficacy endpoints including progression-free survival, PSA progression-free survival, and overall survival are all patients who receive at least one dose of protocol therapy. Criteria for censoring for each of the study endpoints is listed below in Section 8.3.3.

The analysis population for correlative endpoints include all patients who receive at least one dose of protocol therapy who have evaluable correlative sample/data.

8.3.2 Primary Analysis (or Analysis of Primary Endpoints)

The composite response rate is the primary endpoint of the study, defined as:

- ≥ 50% decline from baseline PSA (defined by C1D1 value), confirmed by repeat measurement ≥ 3 weeks later AND/OR
- Objective tumor response by RECIST 1.1 criteria AND/OR

The composite response rate along with 95% confidence interval will be reported.

8.3.3 Secondary Analysis (or Analysis of Secondary Endpoints)

Secondary Objective 1 Analysis: AEs will be recorded and severity-graded using CTCAE version 5.0. Clinically significant laboratory, physical exam, scan, and ECG abnormalities will be captured as AEs. The frequency and severity of AEs will be descriptively reported on a per-patient analysis.

Secondary Objective 2 Analysis: The median radiographic progression-free survival determined by PCWG3 criteria

Secondary Objective 3 Analysis: PSA50 and PSA90 response are defined as above, a ≥ 50% and ≥ 90% decline from baseline in serum PSA, respectively, confirmed by repeat measurement ≥ 4 weeks later. The PSA50 and PSA 90 response proportions will be reported along with 95% confidence interval for each study cohort, for the subset of PSA-evaluable patients (serum PSA ≥ 2 ng/mL at baseline).

Secondary Objective 4 Analysis: Median progression-free survival will be determined for each cohort as from the date of first dose of protocol-defined therapy, using Kaplan-Meier product limit method. Progression is defined as per Section 7.1.4. The first scan time point demonstrating radiographic progression requires confirmatory scans performed ≥ 4 weeks after first scan time point to confirm progression. Patients who discontinue treatment for reasons other than those listed above (e.g. AE, patient withdrawal) will be censored by the date of last treatment.

Secondary Objective 5 Analysis: The median overall survival along with 95% confidence interval will be determined from the date of first dose of protocol-defined therapy until death from any cause, using the Kaplan-Meier product limit method. Patients will be followed for long-term survival as outlined in the Study Procedures. Patients who withdraw from study will be censored for analysis of overall survival using the date of study withdrawal.

Secondary Objective 6 Analysis: The objective response rate and median duration of response will be reported along with 95% confidence interval, for the subset of patients with measurable soft tissue disease by RECIST 1.1 criteria.

8.3.4 Exploratory/Correlative Analysis/Assessments

Exploratory Objective 1 Analysis: To explore the association between baseline metastatic tumor characteristics including t-SCNC, AR, RB1 loss, and immune response transcriptional signatures with clinical outcomes

Exploratory Objective 2 Analysis: To evaluate objective response rate and median progression-free survival by irRECIST criteria

Exploratory Objective 3 Analysis: To evaluate the association between immune related AEs (irAEs) and clinical efficacy outcomes

Exploratory Objective 4 Analysis: To evaluate the association between baseline and change from baseline in circulating T cell and myeloid cell subsets with clinical outcomes

Exploratory Objective 5 Analysis: To explore the mechanism of skin rash in patients receiving combination of apalutamide plus cetrelimab

Exploratory Objective 6 Analysis: To explore the association between genomic and epigenomic features of circulating tumor DNA with clinical outcomes

Exploratory Objective 7 Analysis: To explore the association between circulating tumor cell (CTC) characteristics including heterogeneity, overall CTC count, and expression of markers of interest (AR, CD56, cytokeratin) with clinical outcomes

Quantification of circulating T cell subsets will be performed using mass cytometry analysis of whole blood. The percent change from baseline in the circulating T cell subsets will be reported using descriptive statistics (e.g. median, range, standard deviation). In an exploratory fashion, the study cohort will be dichotomized by those with percent change from baseline above and below median and efficacy outcomes will be compared between dichotomized subgroups using log-rank test for time-to-event endpoints (e.g. PFS, duration of response) and Fisher's exact test for categorical variables (e.g. composite response rate, objective response rate, PSA50 response rate).

Baseline metastatic tumor biopsies will be evaluated for following biomarkers of interest:

- Genomic alterations by targeted next-generation sequencing including presence of *RB1* loss
- Transcriptional profiling and application of previously validated signatures and specific genes implicated with immune response, t-SCNC, RB1 loss, and AR activity
- Histologic assessment for t-SCNC morphology
- When feasible, immunohistochemical analysis to identify PD-L1 expression level and tumor infiltrating lymphocytes

As of Protocol Amendment 1.8 dated 07-24-2023, the italicized analyses below will no longer be performed. Epic Sciences is no longer involved in sample analysis and will return UCSF samples back to UCSF.

Circulating tumor cells be analyzed using the Epic Sciences' platform for the following biomarkers of interest:

- *Heterogeneity score*
- *NEPC probability using previously published prediction tool (Beltran et al. CCR 2015)*
- *Enumeration*
- *Expression of AR, CD56, cytokeratin, and RB1 using IF assays*

Circulating tumor DNA will be analyzed by the Feng laboratory at UCSF for the following biomarkers of interest:

- Genomic alterations by targeted next-generation sequencing including presence of *RB1* loss
- Inference of gene expression of target genes of interest, including AR, EZH1, ASCL1, using 5-hydroxymethyl cytosine (5-hmC) sequencing of ctDNA

The association between the above tissue-based biomarkers (baseline and change from baseline) with clinical efficacy endpoints including PFS, ORR, PSA50, and overall survival will be analyzed using log-rank test for time-to-event endpoints (e.g. PFS, duration of response) and Fisher's exact test for categorical variables (e.g. composite response rate, objective response rate, PSA50 response rate).

The Lymphocyte Proliferation Assay to study mechanism of apalutamide induced rash

The lymphocyte proliferation assay (LPA) allows an assessment of the role of immunological reactions in drug-induced adverse reactions. The assay allows a measurement of the ability of lymphocytes placed in short-term tissue culture to undergo a clonal proliferation when stimulated in vitro by a foreign molecule, antigen or mitogen. Several studies have shown that CD4+lymphocytes proliferate in response to antigenic peptides in association with Class II MHC molecules on antigen-presenting cells. This proliferative response of lymphocytes to antigen in

vitro occurs only if the patient has been immunized to that antigen, either by having recovered from an infection with the microorganism containing that antigen, or by having been vaccinated.

Therefore, some normal individuals may not respond to a given antigen, but most people will respond to at least one of several common microbial antigens.

This study will determine whether subjects who have experienced skin rash while on

apalutamide have an apalutamide (metabolite) specific LPA response. Besides lymphocyte proliferation various other endpoints will be assessed on PBMCs like Elispot. If lymphocyte proliferation is observed, additional studies will be conducted to isolate the individual T-cell clones.

9 Study Management

9.1 Pre-study Documentation

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with GCP and all applicable regulatory requirements.

Before initiating this trial, the PI will have written and dated approval from the Institutional Review Board for the protocol, written informed consent form, subject recruitment materials, and any other written information to be provided to participants before any protocol related procedures are performed on any participants.

The clinical investigation will not begin until either FDA has determined that the study under the Investigational Drug Application (IND) is allowed to proceed or the FDA has determined that the study is exempt from IND requirements.

The PI must comply with the applicable regulations in Title 21 of the Code of Federal Regulations (21 CFR §50, §54, and §312), GCP/ICH guidelines, and all applicable regulatory requirements. The IRB must comply with the regulations in 21 CFR §56 and applicable regulatory requirements.

9.2 Institutional Review Board Approval

The protocol, the proposed informed consent form, and all forms of participant-facing materials related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the UCSF IRB. Prior to obtaining IRB approval, the protocol must be approved by the Helen Diller Family Comprehensive Cancer Center Site Committee and by the Protocol Review Committee (PRC). The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

9.3 Informed Consent

All participants must be provided a consent form describing the study with sufficient information for each participant to make an informed decision regarding their participation. Participants must sign the IRB -approved informed consent form prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

9.4 Changes in the Protocol

Once the protocol has been approved by the UCSF IRB, any changes to the protocol must be documented in the form of an amendment. The amendment must be signed by the PI and approved by PRC and the IRB prior to implementation.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to participants, an amendment may be implemented prior to IRB approval. In this circumstance, however, the PI must then notify the IRB according to institutional requirements.

9.5 Handling and Documentation of Clinical Supplies

The Principal Investigator will maintain complete records showing the receipt, dispensation, return, or other disposition of all investigational drugs at the site. The date, quantity and batch or code number of the drug, and the identification of participants to whom the investigational product has been dispensed by participant number and initials will be included.

The PI at each study site shall not make the investigational drug available to any individuals other than to qualified study participants. Furthermore, the PI at each study site will not allow the investigational product to be used in any manner other than that specified in this protocol.

9.6 Case Report Forms (CRFs)

The PI and/or designee at each study site will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document safety and treatment outcomes for safety monitoring and data analysis. All study data will be entered into OnCore® via standardized CRFs in accordance with the CTMS study calendar, using single data entry with a secure access account. Study personnel for each study site will complete the CRFs; the PI for the study site will review and approve the completed CRFs.

The information collected on CRFs shall be identical to that appearing in original source documents. Source documents will be found in the participant's medical records maintained by study personnel at each study site. All source documentation should be kept in separate research files for each participant.

In accordance with federal regulations, the PI at each study site is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto CRFs. The PI will approve all completed CRFs to attest that the information contained on the CRFs is true and accurate.

The PI at each study site will be responsible for ensuring the accurate capture of study data. At study completion, when the CRFs have been declared to be complete and accurate, the database will be locked. Any changes to the data entered into the CRFs after that time can only be made by joint written agreement among the Study Chair and the trial statistician.

All source documentation and CTMS data will be available for review/monitoring by the UCSF DSMC and regulatory agencies.

9.7 Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center DSMC will be the monitoring entity for this study. The UCSF DSMC will monitor the study in accordance with the NCI-approved Data and Safety Monitoring Plan (DSMP). The DSMC will routinely review all AEs and suspected adverse reactions considered “serious”. The DSMC will audit study-related activities to ensure that the study is conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). Significant results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as applicable. See Appendix 2 - Data and Safety Monitoring Plan.

9.8 Record Keeping and Record Retention

The PI at each study site is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects, as well as written records of the disposition of the drug when the study ends.

The PI at each study site is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the CRFs and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

Study documentation includes all CRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed participant consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

In accordance with FDA regulations, the PI at each study site shall retain records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

9.9 Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the Sponsor-Investigator and collaborators.

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Appendix 1 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 2 (Single Site): Phase II or III Institutional Trial

1. Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) is responsible for auditing data quality and participant safety for all HDFCCC institutional clinical trials. A summary of DSMC activities for this trial includes:

- Semiannual auditing (depending on trial accrual)
- Review of serious adverse events
- Minimum of biennial regulatory auditing

2. Monitoring and Reporting Guidelines

Investigators will conduct a continuous review of data and participant safety at monthly site committee meetings where the results of each participant's treatment are discussed and documented in the site committee minutes.

All institutional Phase II and III therapeutic trials are audited on a semiannual basis, with all data from twenty percent of the enrolled participants audited by the DSMC Monitor/Auditor. The assigned DSMC Monitor/Auditor will review no more than a total of 10 participant charts during the course of auditing this trial. DSMC Monitor/Auditors will send a follow-up report to the study team within 20 business days after the auditing visit is complete for the PI and the study team to resolve all action items from this report within 20 business days. An abbreviated regulatory review (i.e., reviewing protocol and consent versions, SAEs, PVs, DOA logs, 1572 forms, etc.) will occur at each participant monitoring review; however, a full regulatory review will occur on a biennially basis by the DSMC for regulatory compliance.

Auditing of all enrolled participants in these trials will be complete after 20% of enrolled participants have been audited through five cycles of treatment. However, regulatory reviews of the trial, safety reviews (i.e., Serious Adverse Event (SAE) reviews and Protocol Violation (PV) reviews), and audit/inspection preparation (as applicable) will continue until the trial is closed by the IRB.

3. Review and Oversight Requirements

3.1 Adverse Event Monitoring

All Grade 3-5 adverse events (AEs), whether or not considered to be expected or unexpected and whether or not considered to be associated with the use of the investigational agent(s) or study procedure, will be entered into OnCore®, UCSF's Clinical Trial Management System.

Adverse events are graded according to the Common Terminology Criteria for Adverse Events (CTCAE) as developed and revised by the Common Therapy Evaluation Program (CTEP) of the National Cancer Institute. Adverse events are further given an assignment of attribution or relationship to investigational agent or study procedure. Attribution categories are:

- **Definite** – The adverse event is clearly related to the investigational agent(s) or study procedure.
- **Probable** – The adverse event is likely related to the investigational agent(s) or study procedure.

- **Possible** – The adverse event may be related to the investigational agent(s) or study procedure.
- **Unrelated** – the adverse event is clearly not related to the investigational agent(s) or study procedure.

All Grade 3-5 adverse events entered into OnCore® will be reviewed on a monthly basis at the Site Committee meetings. The Site Committee will review and discuss the selected toxicity, the toxicity grade, and attribution assignment.

3.2 Serious Adverse Event Reporting

By definition, an adverse event is defined as a serious adverse event (SAE) according to the following criteria:

- Death.
- Life-threatening (i.e., results in an immediate risk of death).
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Permanent or significant disability/incapacity
- Gives rise to a congenital anomaly/birth defect, or cancer, or any experience that suggests a significant hazard, contraindication, side effect, or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above.
- Event occurring in a gene therapy study.
- Event that changes the risk/benefit ratio of a study.
- Any other event the Principal Investigator judges to be serious or which would suggest a significant hazard, contraindication, side effect, or precaution.

Serious adverse event reporting will be in accordance with all IRB regulations. For trials conducted under an investigational new drug (IND) application, the SAE will be reported in accordance with Code of Federal Regulation Title 21 Part 312.32 and will be reported on a Med Watch form.

UCSF IRB website for guidance in reporting serious adverse events:

https://irb.ucsf.edu/adverse-event

Med Watch forms and information:

www.fda.gov/medwatch/getforms.htm

All serious adverse events are entered into OnCore®, as well as submitted to the IRB (per IRB guidelines). The SAEs are reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at DSMC meetings, which take place every six weeks. The date the SAE is sent to all required reporting agencies will be documented in OnCore®.

If the SAE involves a subject death, and is determined to be possibly, probably or definitely related to the investigational drug or any research related procedure, the event must be reported to the DSMC Chair (or Vice Chair) and DSMC Director within one business day.

3.3 Review of Adverse Event Rates

If an increase in the frequency of Grade 3 or 4 adverse events (above the rate reported in the Investigator Brochure or package insert) is noted in the study, the Principal Investigator will notify the DSMC via report at the time the increased rate is identified. The report will indicate if the incidence of adverse events observed in the study is above the range stated in the Investigator Brochure or package insert.

If at any time the Investigator voluntarily holds enrollment or stops the study due to safety issues, the DSMC Chair (or Vice Chair) and the DSMC Director must be notified within one business day and the IRB must be notified as per IRB reporting regulations.

Data and Safety Monitoring Committee Contacts:

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Appendix 3 Approved Methods of Contraception

To avoid risk of drug exposure through the ejaculate (even men with vasectomies), patients must use a condom during sexual activity while on study drug and for 5 months following the last dose of study drug. Donation of sperm is not allowed during the study and for 5 months following the last dose of study drug.

Maternal use of an anti-androgen is expected to produce changes in hormone levels that may affect fetal development.

If the patient is engaged in sexual activity with a woman of childbearing potential, a condom is required along with another effective contraceptive method consistent with local regulations regarding the use of birth control methods for patients participating in clinical studies and their partners. Highly effective forms of contraception include:

- Established use of oral, injected or implanted hormonal methods of contraception; placement of an intrauterine device (IUD) or intrauterine (IUS) system;
- Barrier methods: condom with spermicidal foam/gel/film/cream/suppository or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository;
- Vasectomy;
- True abstinence (an option when this is in line with the preferred and usual lifestyle of the patient).

Two highly effective forms of contraception are required during the study and for 5 months after the last dose of study drug.

Appendix 4 Prohibited Medications List

Participants are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Antineoplastic systemic chemotherapy or biological therapy other than LHRH analogue
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents not specified in this protocol
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary metastatic lesion or to the brain may be allowed at the investigator's discretion.

Live vaccines within 30 days prior to the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.

COVID-19 vaccine is allowed.

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited during the study, discontinuation from study therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study treatment requires the mutual agreement of the Principal Investigator and subject.

Prohibited Therapies

- Aminophylline/theophylline
- Atypical antipsychotics (e.g., clozapine, olanzapine, risperidone, ziprasidone)
- Bupropion
- Lithium
- Meperidine and pethidine
- Phenothiazine antipsychotics (e.g., chlorpromazine, mesoridazine, thioridazine)
- Tricyclic and tetracyclic antidepressants (e.g., amitriptyline, desipramine, doxepin, imipramine, maprotiline, mirtazapine)
- Systemic immunotherapy or immunosuppressants (e.g., ipilimumab, cyclosporine, infliximab). However, the use of immunosuppressive medications for the management of irAEs, IRRs, or in subjects with contrast allergies is acceptable.
- Live or live attenuated vaccines; annual inactivated influenza vaccine is permitted
- Other anticancer therapies, excluding GnRH analog