CLINICAL PROTOCOL ARV-110-mCRPC-103

A Phase 1b Open-Label, Clinical Trial to Evaluate the Safety, Tolerability, and Pharmacokinetics of ARV-110 in Combination with Abiraterone in Patients with Metastatic Prostate Cancer

Sponsor Name	Arvinas Androgen Receptor, Inc. 5 Science Park 395 Winchester Avenue New Haven, CT 06511
Regulatory Agency Identifying Number(s):	Investigational New Drug Number: 137841 EudraCT: 2021-003046-21
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DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Original Protocol	02-June-2021	Not applicable
Update	29-June-2021	Changed the Sponsor name from Arvinas, Inc. to Arvinas Androgen Receptor, Inc.
Amendment 1.1 (UK)	14-Mar-2022	Added information per MHRA review comments; Incorporation of Protocol Administrative Letter dated 03-Jan-2022
Amendment 1.2 (France)	04-May-2022	Added information per ANSM and CEC review comments; Incorporation of Protocol Administrative letter dated 03-Jan-2022
Amendment 2.0 (Global)	02-Aug-2022	Modified the eligibility criteria, including the requirements for rising PSA values. Updated prohibited medications (proton-pump inhibitors, H2 blockers, antacids). Incorporated Amendment 1.1 and 1.2 changes into global amendment. Updated SAE reporting methods based on new pharmacovigilance vendor.
Amendment 3.0 (Global)	28-Mar-2024	Modified to provide guidance for sites with patients who continue to receive study treatment after the primary study completion date, including a modified patient visit schedule and reduced data collection. • Added SoA Table 5 with schedule of reduced study assessments. • Added Appendix 10 as an index to relevant sections clarified within the protocol, including changes to, drug management, SAE and other safety event reporting, and stopping data entry to the eCRF. Incorporation of Protocol Administrative letters dated 03-Mar-2023 [redacted] change) and 18-Jan-2024 (PK sam [redacted] ation).

1. SYNOPSIS

Protocol Title: A Phase 1b Open-Label, Clinical Trial to Evaluate the Safety, Tolerability, and Pharmacokinetics of ARV-110 in Combination with Abiraterone in Patients with Metastatic Prostate Cancer

Study Phase: 1b

Rationale:

This study will assess the combination of ARV-110 and abiraterone in patients with metastatic prostate cancer with rising prostate-specific antigen (PSA) on abiraterone.

The androgen receptor (AR) pathway is critical for the initiation and progression of prostate cancer. Abiraterone inhibits CYP17, an enzyme necessary for the synthesis of androgens, including testosterone. Abiraterone is approved by the FDA for the treatment of metastatic castration-resistant prostate cancer (mCRPC) and high-risk castrate-sensitive prostate cancer (CSPC). Approximately 10-33% of patients are expected to have primary resistance to abiraterone and nearly all patients will ultimately progress (Antonarakis, 2016; Buttigliero et al., 2015; Fizazi et al., 2017).

Several studies have evaluated the combination of abiraterone and AR inhibition based on the hypothesis of cross-resistance (Simon et al., 2021). Resistance to abiraterone may occur due to increased AR expression and continued AR activity from upregulation of steroid precursors (e.g., progesterone) or exogenous corticosteroids. Resistance to AR inhibitors may occur due to upregulation of androgen synthesis, resulting in AR reactivation.

The Alliance study, A031201, evaluated the combination of abiraterone and enzalutamide vs. enzalutamide in mCRPC patients (Morris, 2019). This study demonstrated that the combination of abiraterone and enzalutamide was tolerable and increased the on-treatment median radiographic progression-free survival (rPFS) from 20.7 to 25.2 months (hazard ratio [HR] 0.85, 95% confidence interval [CI] 0.74-0.97, p=0.02) compared to enzalutamide alone. However, the combination did not improve median overall survival (mOS). More recently, final analysis of the ACIS study demonstrated significant benefit of abiraterone plus apalutamide vs. abiraterone alone in mCRPC patients who progressed on androgen deprivation therapy (ADT; no other prior systemic therapies): rPFS 22.6 vs 16.8 months (HR 0.69, 95% CI 0.58-0.83, p<0.0001), and 30% reduction in death rate with no change in mOS (Rathkopf et al., 2021).

In this study ARV-110, a potent, selective, orally bioavailable, PROteolysis Targeting Chimera (PROTAC®) that induces AR degradation, will be combined with abiraterone at the time patients are beginning to progress on abiraterone, in order to overcome resistance and re-establish AR pathway blockade. Support for the combination of ARV-110 and abiraterone comes from preclinical data (ARV-110 IB, and Section 4.2.2.1). In castrated mice bearing xenografts of vertebral cancer of the prostate (VCaP) cell line, the combination of ARV-110 and abiraterone resulted in improved tumor growth inhibition (TGI) compared to either agent alone.

Furthermore, mice bearing abiraterone-resistant VCaP xenografts demonstrated TGI when treated with ARV-110.

ARV-110 may offer benefits over AR inhibitors when combined with abiraterone. ARV-110 inhibits tumor growth in enzalutamide-resistant and -insensitive xenograft mouse models (see Section 4.2.2.2) and has demonstrated preliminary clinical activity in patients with AR mutations associated with abiraterone resistance in the first in human (FIH) Phase 1/2 study ARV-110-mCRPC-101.

Based on ongoing clinical experience with ARV-110 monotherapy in the FIH study (see Section 4.3) and the safety profile of abiraterone, the Sponsor anticipates that the combination of ARV-110 and abiraterone will have an acceptable safety profile. Overlapping toxicities may include fatigue, nausea, vomiting, diarrhea, and anemia.

Study Population:

Patients with metastatic prostate cancer (mPC) who are currently on abiraterone with rising PSA values and without radiographic progression will constitute the study population (Section 7). To be eligible to participate in this study, patients must meet all the **full** eligibility requirements as defined in the protocol.

Key Inclusion Criteria:

- Histological, pathological, or cytological confirmed diagnosis of adenocarcinoma of the prostate.
- Ongoing treatment with stable doses of abiraterone (on an empty stomach) and a concomitant corticosteroid for mCRPC or metastatic castration-sensitive prostate cancer (mCSPC) until Cycle 1, Day 1 (C1D1). If a patient had treatment interruptions or dose modifications of abiraterone within 2 weeks of C1D1, the Investigator would inform the Medical Monitor (or designee).
- Recent PSA values must demonstrate:
    - Rising PSAs no less than 16 weeks after initiation of abiraterone; and
    - At least 2 rising PSA values that are higher than the PSA nadir on abiraterone, measured at a minimum of 1 week apart. The screening PSA for this study may be used as the 2nd PSA value.
- No known radiographic evidence of disease progression while receiving abiraterone and clinically benefitting at the time of consent. If there is evidence of radiographic disease progression during screening, the patient may be considered eligible if, in the judgement of the investigator, the patient is clinically benefitting from abiraterone.
- Ongoing ADT with a gonadotropin-releasing hormone (GnRH) analogue or inhibitor, or orchiectomy (surgical or medical castration).
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (Appendix 8).

- The following PSA values with dates must be documented in the electronic case report form (eCRF) for all patients:
    - Last PSA prior to initiation of abiraterone
    - PSA nadir while on abiraterone
    - Rising PSAs after at least 16 weeks after initiation of abiraterone (including 2 PSA values at least 1 week apart; the screening PSA for this study may be used as the 2nd PSA value)

Key Exclusion Criteria:

- Previously treated with enzalutamide, apalutamide, darolutamide, or experimental therapies (e.g., protein degraders or inhibitors) directed at the AR.
- Treatment with any chemotherapy, investigational agents, immunotherapy, or hormonal therapy other than GnRH agonists within 28 days of the start of treatment on protocol.
- Radiation therapy within 4 weeks of first dose of study drug or prior irradiation to >25% of the bone marrow. Palliative radiation for the alleviation of pain due to bone metastasis will be allowed during the study.
- Patients taking agents that are either a) sensitive P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), or CYP3A4 substrates, b) P-gp, BCRP, CYP3A4, or CYP2D6 substrates that have a narrow therapeutic index, c) strong CYP3A4 inhibitors or inducers, or d) any other prohibited and/or restricted medications described in Section 8.7.2.
- Major surgery (as judged by the Investigator) within 4 weeks of first dose of study drug.
- Any of the following in the previous 12 months: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure (New York Heart Association class II, III or IV), cerebrovascular accident, transient ischemic attack, symptomatic pulmonary embolism, or other clinically significant episode of thromboembolic disease.
- Any of the following in the previous 6 months: congenital long QT syndrome, Torsade de Pointes, arrhythmias (including sustained ventricular tachyarrhythmia and ventricular fibrillation), left anterior hemiblock (bifascicular block), or ongoing cardiac dysrhythmias of National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE) Grade ≥2, atrial fibrillation of any grade (Grade ≥2 in the case of asymptomatic lone atrial fibrillation).
- Hypertension that cannot be controlled by medications (>150/90 mmHg despite optimal medical therapy).

- Active, uncontrolled bacterial, fungal, or viral infection, including hepatitis B virus, hepatitis C virus, known human immunodeficiency virus (HIV), or acquired immunodeficiency syndrome (AIDS)-related illness. Patients whose viral load is negative or HIV-seropositive patients who are healthy and low risk for AIDS-related outcomes may be considered eligible. HIV-positive patients should be free of any serious AIDS-defining conditions (e.g., opportunistic infections) with an undetectable viral load.
- Active inflammatory gastrointestinal disease, uncontrolled chronic diarrhea, known diverticular disease, or previous gastric resection or lap band surgery. Gastroesophageal reflux disease is allowed provided that treatment with prohibited medications (e.g., proton pump inhibitors) is not required.
- Patients with Child Pugh C.
- Patients with electrolyte imbalances of hypokalemia, hypomagnesemia, and/or hypocalcemia.
- Patients with corrected QT interval by Fredericia's method (QTcF) $\geq$ 470 msec.

Objectives and Endpoints

Objective	Endpoint
Primary	
Evaluate the safety and tolerability of ARV-110 in combination with abiraterone and select the recommended Phase 2 dose (RP2D)/schedule for the combination.	The following safety endpoints will be assessed: • Dose-limiting toxicities (DLTs) in first 4 weeks of the study combination treatment and determination of the RP2D • AEs as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), timing, seriousness, and relationship to study drug combination • Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), and timing
Secondary	
Characterize the pharmacokinetics (PK) of abiraterone when given alone and in combination with ARV-110. Characterize the PK of ARV-110 when given in combination with abiraterone.	The following PK parameters of abiraterone and ARV-110, will be assessed if data allows: AUC_{tau}, AUC_{last}, C_{max}, C_{min}, T_{max}, C_{last}, and T_{last}. See Table 12 for definitions.
Assess preliminary antitumor activity.	Anti-tumor activity of ARV-110 in combination with abiraterone will be assessed by evaluating the following: • Percent of patients with lack of PSA progression • A ≥30% or ≥50% decline in PSA from Cycle 1 Day 1 (baseline) PSA value (PSA30 and PSA50, respectively) response rate and duration • Time to PSA progression • rPFS • Overall response rate (ORR) per modified RECIST 1.1/PCWG3 and duration of response (DOR) in patients with measurable disease at baseline
Exploratory	
[redacted]	

Overall Design:

Number of Patients:

Approximately 40 patients are expected to be treated on study, with an initial safety lead-in consisting of at least 3 evaluable patients. A Safety Review Committee (SRC) will examine all available data from the safety lead-in cohort to determine the recommended Phase 2 dose (RP2D) and before additional patients can be treated.

Study Treatment and Duration:

This study will be open to patients with metastatic adenocarcinoma of the prostate with rising PSA while receiving abiraterone treatment.

All patients will receive ARV-110 orally (PO) daily, abiraterone PO daily, and a corticosteroid. Patients in the initial safety lead-in will be dosed with 420 mg daily of ARV-110, 1000 mg daily or less of abiraterone (the same dose they were on prior to study enrollment), and a concomitant corticosteroid to be dosed at the discretion of the Investigator.

ARV-110 is an in vitro inducer of CYP3A4 and abiraterone is a CYP3A4 substrate and as such abiraterone exposure may be reduced when given with ARV-110. Cycle 1 pharmacokinetic (PK) data from the patients in the safety lead-in will determine the impact, if any, of ARV-110 on reducing the level of abiraterone via CYP3A4 induction. Based on the results of the safety lead-in, the dose of abiraterone or ARV-110 may be adjusted as appropriate for patients already on trial, as well as the newly enrolled patients.

As per local label, abiraterone must be taken on an empty stomach with water at least 1 hour before or 2 hours after a meal. Patients will also take ARV-110 at 420 mg by mouth once daily (QD) with food (meal of ≥400 calories that includes a mixture of fat, carbohydrates, and protein). It is recommended that patients take ARV-110 with the largest meal of the day (e.g., dinner), except for days when PK sampling is performed in the clinic. Patients may continue ARV-110 and abiraterone treatment at the discretion of the Principal Investigator until progression of disease, the occurrence of a treatment-emergent adverse event (TEAE) warranting discontinuation, death, withdrawal of patient consent, or when patients meet study drug stopping criteria for individual patients.

Statistical Considerations

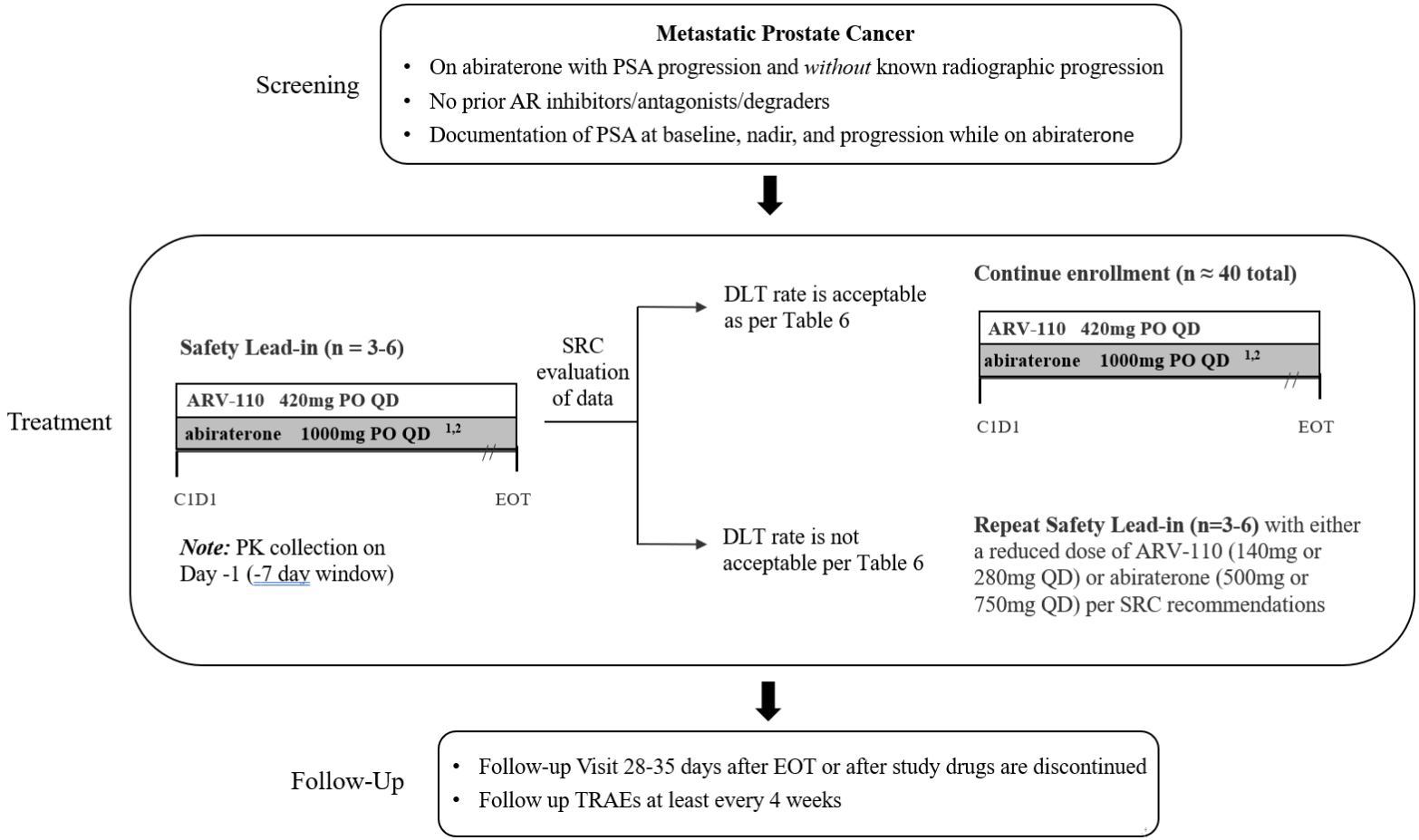
Approximately 40 patients will be treated to evaluate the safety profile and preliminary antitumor activity of ARV-110 in combination with abiraterone in patients with mPC with rising PSA on abiraterone. Assuming the target PSA control rate (as measured by lack of PSA progression at 12 weeks) ranges from 30% to 90%, the width of corresponding 95% CIs per the Clopper-Pearson exact method will be 0.21 to 0.33. A detailed table is provided in Table 13.

Patients whose screening scans show radiographic progression (compared to the last scans obtained prior to study enrollment) may be replaced to ensure a minimum of 40 study patients with PSA-only progression on abiraterone.

The RP2D will be based on safety and available PK data from the safety-lead in. AEs and serious adverse events (SAEs) will be tabulated by system organ class and preferred terms. Laboratory test results after the first dose of ARV-110 in combination with abiraterone will be summarized with regard to shifts from baseline values. All AEs will be graded according to NCI CTCAE version 5.0.

Details of the statistical analyses will be provided in the study's statistical analysis plan (SAP) and will further describe the analysis of all clinical, safety, PK and laboratory data collected for the study.

2. STUDY SCHEMA



1. The abiraterone dose will be either 1000 mg daily or the dose the patient was receiving immediately prior to study enrollment.
2. If abiraterone exposure reduces by approximately 50% or more in the safety lead-in, the frequency of abiraterone administration may be increased to twice daily (BID) based on SRC recommendation. The decision to increase the frequency of abiraterone will be based on the totality of available pharmacokinetic (PK) and safety data.

3. SCHEDULE OF ACTIVITIES

The following tables provide an overview of the visits and procedures for:

- Screening (Table 1)
- On-Treatment Activities (up to Notice from Sponsor of Primary Study Completion) (Table 2)
- Intensive PK and ECG for Selected Patients in Safety Lead-In (Table 3) (this cohort closed in December 2022)
- Sparse PK and ECG for All Other Patients (up to 18-Jan-2024) (Table 4)
- Schedule of Activities after notice from Sponsor of primary study completion (Table 5)

Note: After notice from Sponsor of primary study completion, clinical data will no longer be recorded in the eCRF. Clinical data will be recorded only in the site source. For modified collection and reporting of AEs, see Section 10.2 and Reporting of SAEs, Deaths Due to Disease Progression, and AEs Leading to Discontinuation of Study Drug After Notice From Sponsor of Primary Study Completion in Appendix 5.

Table 1. Screening Activities

Procedure [a]	Notes All items to be performed within 28 days of C1D1 unless otherwise noted.
Informed consent	Obtain prior to performing testing for eligibility. Register in IRT system to obtain patient number.
Inclusion/exclusion criteria	See Sections 7.1 and 7.2
Medical history	Include disease process (e.g., staging) and concurrent illness, prior treatments, and any current medical treatments for any condition.
Contraception check	Discuss with patient the need to use 2 highly effective contraception methods consistently and correctly.
Full physical examination, vital signs, and performance status	Includes height, weight, ECOG performance status (see Appendix 8), temperature, blood pressure (BP), heart rate, and respiratory rate (RR) (record in sitting position after 5 min rest)
ECG	Screening ECG will be a single 12-lead ECG.
Review of concomitant medications	All medications including over-the-counter medications and/or herbal supplements taken up to 28 days prior to consent.
Assessment of signs and symptoms	All baseline complaints and/or symptoms.
Hematology	CBC with differential, platelets, RBC.
Chemistry	AST, ALT, ALP, BUN/urea, creatinine, creatinine kinase [b], Cl, K, Mg, Na, total Ca, total bilirubin [c], LDH, total protein, albumin, uric acid, amylase, C-reactive protein, CO_2 (bicarbonate), phosphorus/phosphate, glucose (non-fasting).
Coagulation	PT (optional), PTT/APTT, INR.

Procedure [a]	Notes All items to be performed within 28 days of C1D1 unless otherwise noted.
Serum testosterone	Measured using ultrasensitive testosterone assays with a sensitivity of 1 to 2 ng/dL.
Thyroid function	Thyroid function (i.e., thyroid-stimulating hormone).
Urinalysis	Urine dipstick testing is acceptable.
Viral disease screening	Hepatitis B virus surface antigen, hepatitis B core antibody, hepatitis B surface antibody, hepatitis C virus antibodies. HIV testing if required by local regulations. Within 30 days prior to C1D1. See coronavirus disease 19 (COVID) information in Appendix 9.
Baseline disease assessment CT/MRI	Include all known or suspected disease sites. Imaging will include chest, abdomen, and pelvis CT or MRI. Refer to Section 10.4 of protocol.
Bone scan	Within 30 days prior to C1D1. Refer to Sections 7, 10.4, and Appendix 7 for additional instructions on imaging assessments and eligibility.
PSA	PSA must be collected with screening labs. The following PSA values (prior to enrollment) must be documented in eCRF: PSA prior to start of abiraterone, PSA nadir on abiraterone, rising PSAs at least 16 weeks after initiation of abiraterone (including 2 PSA values at least 1 week apart; the screening PSA for this study may be used as the 2nd PSA value).
[redacted]	

Abbreviations: ALP=alkaline phosphatase; ALT=alanine aminotransferase; APTT=activated partial thromboplastin time; AST=aspartate aminotransferase; BP=blood pressure; BUN=blood urea nitrogen; C1D1=Cycle 1, Day 1; CBC=complete blood count; CT=computed tomography; [redacted]; ECG=electrocardiogram; eCRF=electronic case report form; ECOG=Eastern Cooperative Oncology Group; HIV=human immunodeficiency virus; INR=international normalized ratio; IRT=interactive response technology; LDH=lactate dehydrogenase; MB=myocardial band; MRI=magnetic resonance imaging; PSA=prostate-specific antigen; PT=prothrombin time; PTT=partial thromboplastin time; RBC=red blood cell; RR=respiratory rate.

a Some of the assessments referred to in this section may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

b Creatine kinase MB fraction will be performed if clinically indicated.

c Direct, conjugated, and unconjugated bilirubin will be performed if clinically indicated. Unconjugated bilirubin can be derived from total and conjugated bilirubin.

Table 2. Schedule of On-Treatment Activities (up to Notice from Sponsor of Primary Study Completion)

Procedures	**Study Treatment Period**									**Notes**
	Cycle 1 (one cycle = 28 days)				**Cycle 2**		**Cycle 3 and Beyond**	**EOT [1]**	**Follow-Up (28 to 35 days)[2]**	
Treatment Day (Visit Window)	**Day 1**	**Day 8 (±2)**	**Day 15 (±2)**	**Day 21 (±2)**	**Day 1 (±2)**	**Day 15 (±2)**	**Day 1 (±2)**			
Treatment assignment	X									May occur up to 7 days prior to patient's Day 1 visit to allow for drug preparation.
Full PE	X							X		PEs may be performed within 48 hours prior to a scheduled visit. No need to repeat PE if screening PE is within 96 hours of C1D1. An abbreviated PE will be symptom-directed.
Abbreviated PE		X	X	X	X	X	X		X	
Weight	X				X		X	X		
Vital signs	X	X	X	X	X	X	X	X		Temperature, BP, heart rate, RR (record in sitting position after 5 min rest). On clinic days perform pre-dose.
ECOG status	X		X		X	X	X	X	X	See ECOG PS Appendix 8
Hematology	X		X		X	X	X	X		CBC with diff, platelets, RBC. See Appendix 4. No need to repeat on C1D1 if screening assessment performed within 72 hours prior. Perform within 48 hours prior to visits with dosing.
Blood chemistry	X		X		X	X	X	X		AST, ALT, ALP, BUN/urea, creatinine, Cl, K, Na, total Ca, Tbil, TProtein, albumin, CO_2 (bicarbonate), glucose (non-fasting). See Section 10.1.4 of the protocol and Appendix 4. No need to repeat on C1D1 if screening assessment performed within 7 days prior.

Procedures	**Study Treatment Period**									**Notes**
	Cycle 1 (one cycle = 28 days)				**Cycle 2**		**Cycle 3 and Beyond**	**EOT [1]**	**Follow-Up (28 to 35 days)[2]**	
Treatment Day (Visit Window)	**Day 1**	**Day 8 (±2)**	**Day 15 (±2)**	**Day 21 (±2)**	**Day 1 (±2)**	**Day 15 (±2)**	**Day 1 (±2)**			
Additional blood chemistry					X		X			Creatinine kinase, Mg, C reactive protein, amylase, uric acid, LDH, phosphorus/phosphate.
Coagulation	X				X		X	X		PT (optional), PTT/APTT, INR. See Appendix 4. No need to repeat on C1D1 if screening assessment performed within 72 hours prior.
Urinalysis	X							X		Urine dipstick testing is acceptable. No need to repeat on C1D1 if screening assessment performed within 7 days prior.
PSA	X			X	X	X	X	X		
ECG (pre-dose)	X			X	X		X	X		On C1D1, ECG must be performed in triplicate. At all other timepoints, triplicate ECGs must be performed if clinically indicated. On study, if the mean QTcF is prolonged (≥45 msec from the baseline or >500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation. Additional ECGs may be performed as clinically indicated.

Procedures	**Study Treatment Period**									**Notes**
	Cycle 1 (one cycle = 28 days)				**Cycle 2**		**Cycle 3 and Beyond**	**EOT [1]**	**Follow-Up (28 to 35 days)[2]**	
Treatment Day (Visit Window)	**Day 1**	**Day 8 (±2)**	**Day 15 (±2)**	**Day 21 (±2)**	**Day 1 (±2)**	**Day 15 (±2)**	**Day 1 (±2)**			
ECG (post-dose)	X									Triplicate ECGs to be performed 6 hours (±2 hour window) post ARV-110 administration in conjunction with PK sampling (See Table 3 and Table 4 for timepoint collection). If the mean QTcF is prolonged (≥45 msec from the baseline or >500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation. Additional ECGs may be performed as clinically indicated.
ARV-110 administration	(once oral daily beginning on **Day 1**)									Recommended to be taken with the largest meal of the day (e.g., dinner; meal of ≥400 calories that includes a mixture of fat, carbohydrates, and protein). See Section 8.2 of the protocol for administration instructions. Patients must refrain from eating prior to their clinic visit on days indicated in Table 3 and Table 4.
Abiraterone + a concomitant corticosteroid administration	(once oral daily beginning on **Day 1**)									Must be taken on an empty stomach, at least 1 hour before or at least 2 hours after a meal, as per administration instructions found in local label/guidelines.

Procedures	**Study Treatment Period**									**Notes**
	Cycle 1 (one cycle = 28 days)				**Cycle 2**		**Cycle 3 and Beyond**	**EOT [1]**	**Follow-Up (28 to 35 days)[2]**	
Treatment Day (Visit Window)	**Day 1**	**Day 8 (±2)**	**Day 15 (±2)**	**Day 21 (±2)**	**Day 1 (±2)**	**Day 15 (±2)**	**Day 1 (±2)**			
Compliance/ patient diary	X	X	X	X	X	X	X	X		Confirm and reconcile return of all bottles and remaining tablets of ARV-110/abiraterone, as well as the completed patient diary. See Section 8.5 of the protocol.
CT/MRI scans	Every 8 weeks from C1D1 (i.e., Days 56, 112, and 168 [±5 days]) then every 12 weeks (±5 days) thereafter							X		Imaging CT or MRI scans will include chest, abdomen, pelvis and all known or suspected disease sites. See Section 10.4 of the protocol.
Bone scan	Every 8 weeks from C1D1 (i.e., Days 56, 112, and 168 [±5 days]) then every 12 weeks (±5 days) thereafter							X		
[redacted]										
AE/SAE monitoring	X	X	X	X	X	X	X	X	X [3]	See Section 10.2 of the protocol.
Concomitant treatment(s)	X	X	X	X	X	X	X	X	X	See Section 8.7 of the protocol.

Procedures	Study Treatment Period									Notes
	Cycle 1 (one cycle = 28 days)				Cycle 2		Cycle 3 and Beyond	EOT [1]	Follow-Up (28 to 35 days)[2]	
Treatment Day (Visit Window)	**Day 1**	**Day 8 (±2)**	**Day 15 (±2)**	**Day 21 (±2)**	**Day 1 (±2)**	**Day 15 (±2)**	**Day 1 (±2)**			
PK sampling										See Table 3 andTable 4 for timepoint collection and details. Of note, PK samples will be collected on Day -1 (-7-day window) only for patients in the safety lead-in as indicated in Table 3. **Note: PK sample collections are discontinued. Please refer to administrative letter dated 18-Jan-2024 for additional details.**

Abbreviations: AE=adverse event; ALP=alkaline phosphatase; ALT=alanine aminotransferase; APTT=activated partial thromboplastin time; AST=aspartate aminotransferase; BP=blood pressure; BUN=blood urea nitrogen; C1D1=Cycle 1, Day 1; CBC=complete blood count; CT=computed tomography; [redacted] ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=End of Treatment; INR=international normalized ratio; LDH=lactate dehydrogenase; min=minute(s); MRI=magnetic resonance imaging; PE=physical examination; PK=pharmacokinetic(s); PSA=prostate-specific antigen; PT=prothrombin time; PTT=partial thromboplastin time; QTcF=corrected QT interval by Fridericia's method; RBC=red blood cell; RR=respiratory rate; SAE=serious adverse event; Tbil=total bilirubin.
Note: Assessments should be performed prior to dosing on the visit day unless otherwise indicated. On mornings where patients are in the clinic, they will be instructed to hold their dose, which will be administered by study staff on-site. Acceptable time windows for performing each assessment are described in the column headers.

1 End of Treatment/Withdrawal: Visit to be performed as soon as possible but no later than 4 weeks from the last dose of study drug and prior to initiation of any new antitumor therapy. Obtain assessments if not completed during the previous 4 weeks on study. **For patients staying on treatment after notice from Sponsor of primary study completion, please refer to Table 5 for EOT assessment guidelines.**

2 Follow-up: At least 28 days, and no more than 35 days after discontinuation of study drug treatment, patients will return to undergo review of concomitant medications, ECOG performance status, abbreviated PE, and assessment for resolution of any treatment-related toxicity. Patients continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the Investigator, that no further change is expected.

3 Patients continuing to experience treatment-related toxicity will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the Investigator, that no further improvement is expected.

Table 3. Intensive Pharmacokinetic Sampling and ECG Schedule: Selected Patients/Sites (for Patients in Safety Lead-In)*

Note: This cohort closed in December 2022

Procedures	Study Treatment Period				EOT / Withdrawal
		Cycle 1		Cycles 2 and Beyond	
Visit Identifier (Visit Window)	**Day -1 [a] (-7 days)**	**Day 1 [b]**	**Day 21 [b] (±2)**	**Day 1 [b] (±2)**	
Abiraterone Treatment	X	**ARV-110 and Abiraterone (IMP) will start on C1D1. Prior to C1D1 patients will be on abiraterone as part of standard of care.**			
ARV-110 Treatment					
Abiraterone/ARV-110 PK Sampling					
Pre-Abiraterone dose PK	X		X	X	X
1 hour post Abi (±15 min) PK	X		X	X	
2 hours post Abi (±15 min) PK	X		X		
4 hours post Abi (±15 min) PK	X		X		
6 hours post Abi (±15 min) PK	X		X		
8 hours post Abi (±15 min) PK	X		X		
Paired PK Sampling and ECGs					
Pre ARV-110 dose PK and ECGs		X [c]			
6 hours post ARV-110 (±2 hours) PK and ECGs		X [c]			

Abbreviations: Abi=abiraterone; C1D1=Cycle 1, Day 1; ECG=electrocardiogram; EOT=End of Treatment; IMP=investigational medicinal product; min=minute(s); PK=pharmacokinetic(s); SRC=Safety Review Committee.

***** Intensive PK sampling may be performed on patients outside the safety lead-in per SRC recommendations.

Note: On days of scheduled clinic visits for PK, patients must take both study drugs in the clinic.

a On Day -1, abiraterone will be administered on an empty stomach as described in the locally approved label (at least 1 hour before a meal or 2 hours after a meal)

b On C1D1, C1D21 and Day 1 of all subsequent cycles, abiraterone will be administered first on an empty stomach, **and then, at least 1 hour after the abiraterone dose**, a PK sample will be collected. Once PK sample is taken, ARV-110 will be administered with a meal. The 1-hour post-dose sample on these days should be taken prior to ARV-110 dose administration.

c 12-lead ECGs will be performed in triplicate before the pre- and post-dose PK sampling.

Table 4. Sparse Pharmacokinetic Sampling and ECG Schedule: All Other Patients (up to 18-Jan-2024)

Note: PK sample collections are discontinued. Please refer to administrative letter dated 18-Jan-2024 for additional details.

Procedures	Study Treatment Period			EOT / Withdrawal
	Cycle 1		Cycles 2 and Beyond	
Visit Identifier (Visit Window)	**Day 1**	**Day 21 (±2)**	**Day 1 (±2)**	
Pre-abiraterone dose PK	X	X	X	X
Pre ARV-110 dose PK and ECGs [a]	X [b]	X	X	X
6 hours post ARV-110 (±2 hours) PK and ECGs	X [b]			

Abbreviations: C1D1=Cycle 1, Day 1; ECG=electrocardiogram; EOT=End of Treatment; PK=pharmacokinetic(s).

Note: On days of scheduled clinic visits for PK, patients should be instructed to not take their study drug treatment at home, and that it will be given in the clinic.

a On Days 1 and 21 of Cycle 1, and Day 1 of all subsequent cycles, abiraterone will be administered first on an empty stomach, and then at least 1 hour after the abiraterone dose, a PK sample is to be collected. Once PK sample is taken, ARV-110 will be administered with a meal.

b On C1D1, 12-lead ECGs will be performed in triplicate before the pre- and post-dose PK sampling.

Table 5. Schedule of Activities after Notice from Sponsor of Primary Study Completion

Procedures	Study Treatment Period		Follow-Up (28 to 35 days) [3]	Notes
	Every 90-day cycles [1]	EOT [2]		**This table is only applicable for patients who continue study treatment after notice of primary study completion.** **Clinical data will no longer be recorded in the eCRF but will be recorded in the site source.**
Treatment Day (Visit Window)	**Day 1** **(+/-14)**			
Standard of Care Clinical, Laboratory, and Imaging Assessments	See notes to right			PE, weight, vital signs, ECOG, laboratory values, PSA, ECG assessed only as clinically indicated per PI/site standard of care and documented in site source, but not collected by the Sponsor. Tumor imaging will be performed according to site standard of care and documented in site source, but not collected by the Sponsor.
Manual drug dispensation	X			Refer to updated Pharmacy Manual
ARV-110 administration	(once oral daily)			Recommended to be taken with the largest meal of the day (e.g., dinner; meal of ≥400 calories that includes a mixture of fat, carbohydrates, and protein). See Section 8.2 of the protocol for administration instructions. Patients are to take study drug at home.
Abiraterone + a concomitant corticosteroid administration	(once oral daily)			Must be taken on an empty stomach, at least 1 hour before or at least 2 hours after a meal, as per administration instructions found in local label/guidelines. Patients are to take study drug at home.
Compliance/accountability	X	X		Confirm and reconcile return of all bottles and remaining tablets of ARV-110/abiraterone. See Sections 8.4 and 8.6.1 of the protocol.
AE/SAE monitoring, AEs leading to discontinuation of study drug, deaths due to disease progression	X	X	X	See Section 10.2.1.1 of the protocol.

Procedures	Study Treatment Period		Follow-Up (28 to 35 days) [3]	Notes
	Every 90-day cycles [1]	EOT [2]		**This table is only applicable for patients who continue study treatment after notice of primary study completion.** **Clinical data will no longer be recorded in the eCRF but will be recorded in the site source.**
Treatment Day (Visit Window)	**Day 1** **(+/-14)**			
Concomitant treatment(s)	See notes to right			Collected in site source documents only (and on SAE form, if applicable)
EOT checklist		X		EOT Checklist is a paper form to be provided to sites and submitted back to Sponsor at time of EOT. Any questions can be directed to Sponsor per Study Contact List.

Abbreviations: AE=adverse event; ECG=electrocardiogram; eCRF=electronic case report form; ECOG=Eastern Cooperative Oncology Group; EOT=End of Treatment; PE=physical examination; PSA=prostate-specific antigen; SAE=serious adverse event.

Note Acceptable time windows for performing each assessment are described in the column headers.

1 Patient can be seen more frequently as clinically indicated (e.g., for AEs and /or suspicion of disease progression).

2 End of Treatment/Withdrawal: Visit to be performed as soon as possible but no later than 4 weeks from the last dose of study drug and prior to initiation of any new antitumor therapy.

3 Follow-up: At least 28 days, and no more than 35 days after discontinuation of study drug treatment, patients will return to undergo review of concomitant medications, ECOG performance status, abbreviated PE, and assessment for resolution of any treatment-related toxicity and documented in the site source. Patients continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the Investigator, that no further change is expected.

4. INTRODUCTION

4.1 STUDY RATIONALE

This study will assess the combination of ARV-110 and abiraterone in patients with metastatic prostate cancer (mPC) with rising prostate-specific antigen (PSA) values on abiraterone.

The androgen receptor (AR) pathway is critical for the initiation and progression of prostate cancer. Abiraterone inhibits CYP17, an enzyme necessary for the synthesis of androgens, including testosterone. Abiraterone is approved by the United States (US) Food and Drug Administration (FDA) for the treatment of metastatic castration-resistant prostate cancer (mCRPC) and high-risk castrate-sensitive prostate cancer (CSPC). Approximately 10-33% of patients are expected to have primary resistance to abiraterone and nearly all patients will ultimately progress (Antonarakis, 2016; Buttigliero et al., 2015; Fizazi et al., 2017).

Several studies have evaluated the combination of abiraterone and AR inhibition based on the hypothesis of cross-resistance (Simon et al., 2021). Resistance to abiraterone may occur due to increased AR expression and continued AR activity from upregulation of steroid precursors (e.g., progesterone) or exogenous corticosteroids which can activate certain mutant forms of AR. Resistance to AR inhibitors may occur due to upregulation of androgen synthesis, resulting in AR reactivation.

The Alliance study, A031201, evaluated the combination of abiraterone and enzalutamide vs. enzalutamide in mCRPC patients (Morris, 2019). This study demonstrated that the combination of abiraterone and enzalutamide was tolerable and increased the on-treatment median radiographic progression-free survival (rPFS) from 20.7 to 25.2 months (hazard ratio [HR] 0.85, 95% confidence interval [CI] 0.74-0.97, p=0.02) compared to enzalutamide alone. However, the combination did not improve median overall survival (mOS). More recently, final analysis of the ACIS study demonstrated significant benefit of abiraterone plus apalutamide vs. abiraterone alone in mCRPC patients who progressed on androgen deprivation therapy (ADT; no other prior systemic therapies): rPFS 22.6 vs 16.8 months (HR 0.69, 95% CI 0.58-0.83, p <0.0001), and 30% reduction in death rate with no change in mOS (Rathkopf et al., 2021).

In this study ARV-110, a potent, selective, orally bioavailable, PROteolysis Targeting Chimera (PROTAC®) that induces AR degradation, will be combined with abiraterone at the time patients are beginning to progress on abiraterone, in order to overcome resistance and re-establish AR pathway blockade. Support for the combination of ARV-110 and abiraterone comes from preclinical data (ARV-110 IB, and Section 4.2.2.1). In castrated mice bearing xenografts of the vertebral cancer of the prostate (VCaP) cell line, the combination of ARV-110 and abiraterone resulted in improved tumor growth inhibition (TGI) compared to either agent alone. Furthermore, mice bearing abiraterone-resistant VCaP xenografts demonstrated TGI when treated with ARV-110.

ARV-110 may offer benefits over AR inhibitors when combined with abiraterone. ARV-110 inhibits tumor growth in enzalutamide-resistant and -insensitive xenograft mouse models (see Section 4.2.2.2) and has demonstrated preliminary clinical activity in patients with AR mutations associated with abiraterone resistance in the first in human (FIH) Phase 1/2 study ARV-110-mCRPC-101.

Based on ongoing clinical experience with ARV-110 monotherapy in the FIH study (see Section 4.3) and the safety profile of abiraterone, the Sponsor anticipates that the combination of ARV-110 and abiraterone will have an acceptable safety profile. Overlapping toxicities may include fatigue, nausea, vomiting, diarrhea and anemia

4.2 BACKGROUND

4.2.1 Prostate Cancer Background

Globally, prostate cancer is the second most frequent cancer and the fifth leading cause of cancer death in men, with an estimated 1.4 million new cases and 375,000 deaths worldwide in 2020 (Sung, 2021). Patients with mPC have incurable disease with a median 5-year survival of approximately 32.3% (NCI SEER, 2022). These cancers pose a therapeutic challenge and progress despite castrate levels of testosterone; however, most remain dependent on AR signaling as evidenced by rising PSA levels and acquisition of AR gene amplifications and mutations.

Treatment and sequencing of drugs for advanced/metastatic prostate cancer depends on a variety of factors, including hormone sensitivity, tumor burden, and aggressiveness of the disease. For patients without homologous recombination mutations, treatment options for mPC include AR antagonists (e.g., enzalutamide), inhibitors of androgen biosynthesis (abiraterone), Radium 223 (for bone metastases), and chemotherapy (e.g., taxanes).

In patients who have progressed on abiraterone, the efficacy of enzalutamide is limited, with a ≥30% decline in PSA from Cycle 1 Day 1 (baseline) PSA value (PSA_{30}) responses occurring in 36% of patients (Khalaf et al., 2019), and a ≥50% decline in PSA from Cycle 1 Day 1 (baseline) PSA value (PSA_{50}) responses occurring in up to 23% of patients (de Wit et al., 2019). Similarly, docetaxel leads to confirmed PSA_{50} responses in about 26% of patients after progression on abiraterone (de Bono et al., 2017).

A significant unmet medical need persists for mPC despite available therapies, and novel treatments are needed.

4.2.2 ARV-110

Arvinas' PROTAC® technology platform provides a means of marking specific disease-causing cellular proteins for destruction utilizing the cell's normal degradation machinery, the ubiquitin-proteasome system. Specifically, PROTACs are bifunctional small molecules that contain a ligand to a specific target protein connected to a ligand that binds to an E3 ligase, an enzyme that adds the polypeptide ubiquitin to proteins that are to be degraded. The chimeric nature of

PROTACs allows them to recruit an E3 ligase to the target protein, resulting in the ubiquitination and subsequent proteasome-mediated degradation of the target protein.

ARV-110 is a potent, selective, orally bioavailable, PROTAC® small molecule that induces the degradation of the AR. In nonclinical studies using prostate cancer models, ARV-110 demonstrated antitumor activity in multiple xenograft tumor models, including AR gene-amplified, AR mutant and enzalutamide-resistant and -insensitive models (see Section 4.2.2.2). ARV-110 leads to degradation of wild-type AR as well as the AR mutants T878A, H875Y, F877L, and M896V. However, it does not lead to degradation of the AR mutant L702H and the AR-V7 splice variant. Preclinical data also suggests an additive or synergistic effect when ARV-110 is combined with abiraterone (see Section 4.2.2.1).

The FIH study, a Phase 1/2, open-label, dose escalation, and cohort expansion clinical trial to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics of ARV-110 in patients with mCRPC, is currently ongoing. Preliminary analyses suggest a tolerable safety profile and early evidence of clinical activity (see the ARV-110 Investigator's Brochure [IB]).

Dose-related increase in exposure of ARV-110 was observed up to 420 mg total daily dose. Doses ≥420 mg resulted in average area under the plasma concentration-time curve $(AUC)_{0-24}$ above the preclinical efficacy thresholds, based on an enzalutamide-resistant castration-resistant prostate cancer (CRPC) model in mice (3 mg/kg with AUC_{0-24}=8160 ng·hr/mL). Safety was confirmed at doses up to 630 mg. The most common treatment-related adverse events (TRAEs) were nausea, fatigue, diarrhea, vomiting, alopecia, increased aspartate aminotransferase (AST), decreased appetite, and anemia.

A daily dose of 420 mg was selected as the recommended Phase 2 dose (RP2D) for ARV-110.

Additional information on ARV-110 can be found in the IB.

4.2.2.1 Preclinical Data on ARV-110 Plus Abiraterone

The efficacy of ARV-110 and abiraterone was assessed in a 3-phase study using castrated mice bearing human VCaP tumor xenografts. Phase I evaluated the efficacy of single agents and the combination regimen. In Phase II, mice in the abiraterone arm were continuously dosed until the tumors became abiraterone resistant. Phase III then assessed the efficacy of ARV-110 in the abiraterone-resistant tumors.

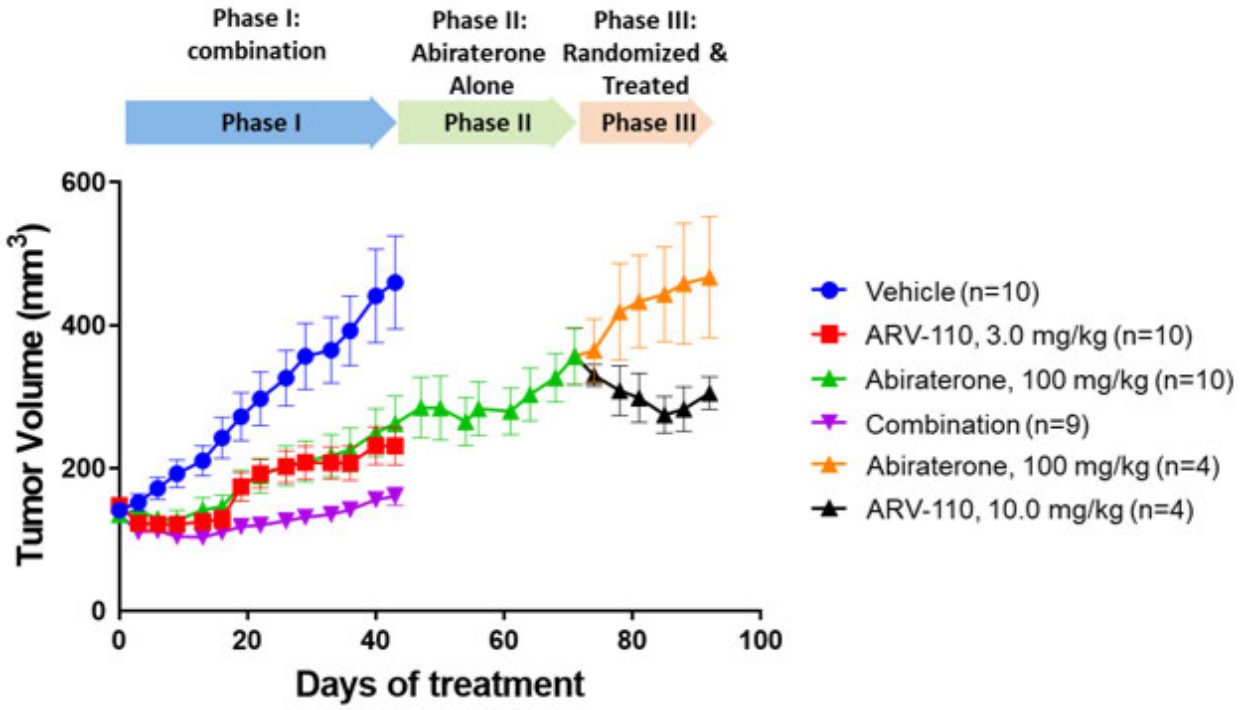
For the first phase of the study, surgically castrated CB17/scid male mice with subcutaneously implanted VCaP tumors in the dorsal flank were treated with single agent ARV-110 (3 mg/kg) or abiraterone (100 mg/kg), or a combination of both agents by oral gavage once daily. As single agents, ARV-110 and abiraterone demonstrated significant TGI, 74% and 60%, respectively. Notably, the combination of these agents demonstrated more robust TGI (92%) than either single agent alone (Figure 1, Phase I). These data suggest that combining ARV-110 with abiraterone may provide additional benefit over either agent alone.

For the third phase of the study, animals with abiraterone-resistant tumors generated in Phase II were randomized when those tumors reached the size of the tumors in the vehicle arm at the end of the Phase I portion of the study. The animals were then treated with either 10 mg/kg ARV-110 or 100 mg/kg abiraterone by oral gavage once daily. As shown in Figure 1 (Phase III), TGI was observed in ARV-110 treated animals bearing abiraterone-resistant tumors.

These data suggest that ARV-110 treatment may provide benefit in patients with CRPC whose tumors have progressed on abiraterone.

During the treatment period, animals tolerated all regimens well as determined by body weight.

Figure 1. Tumor Growth Inhibition of Human VCaP Tumor Xenografts by the Combination of ARV-110 and Abiraterone and of Abiraterone-resistant VCaP Xenografts by ARV-110 in Castrated Mice



4.2.2.2 In Vivo Data on ARV-110 in Enzalutamide-resistant Models

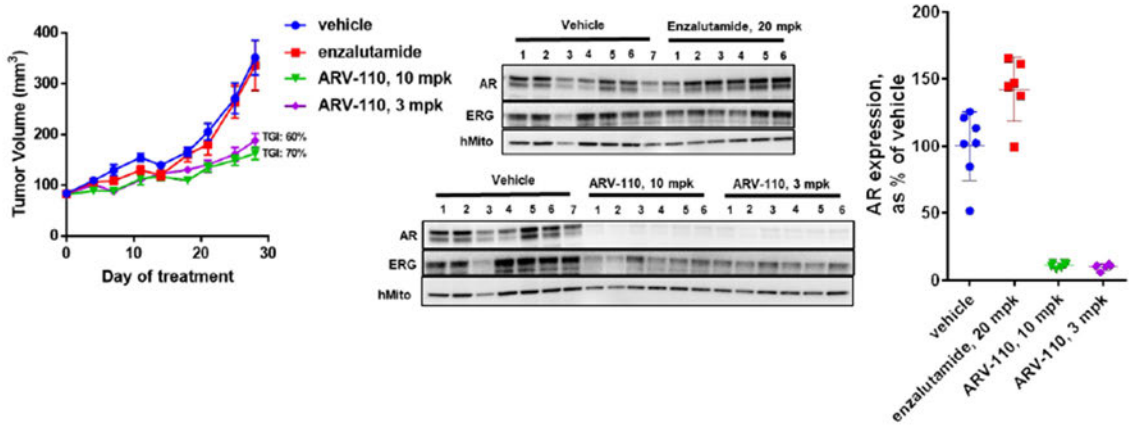
ARV-110 demonstrated TGI in enzalutamide-resistant VCaP xenograft and patient-derived xenograft (PDX) models (see IB for additional information).

VCaP Xenografts

A cohort of 45 enzalutamide-resistant tumor-bearing mice were segregated into 4 arms to receive daily vehicle (PEG300/propylene glycol/D5W 50:30:20; n=10), enzalutamide (20 mg/kg; n=15), ARV-110 (10 mg/kg; n=10), or ARV-110 (3 mg/kg; n=10) via oral gavage. As shown in Figure 2, both 3 mg/kg and 10 mg/kg ARV-110 demonstrated significant TGI, 60% and 70%, respectively, whereas TGI was not observed in the enzalutamide arm, as expected. At the end of

the study, the tumors were excised and subjected to analysis by western blotting for AR levels and related downstream signaling targets Erg and FKBP5. Robust (>90%) AR degradation was observed with 3 mg/kg and 10 mg/kg doses of ARV-110 (Figure 2). Concomitant reductions in AR target genes Erg (due to translocation between AR target gene TMPRSS2 and Erg in VCaP cells) and FKBP5 (not shown) were also observed in the tumors, while this effect did not occur upon enzalutamide treatment. In summary, ARV-110 robustly degraded AR, inhibited AR signaling, and inhibited tumor growth in a model that mimics acquired enzalutamide resistance.

Figure 2. ARV-110 Demonstrated Significant Tumor Growth Inhibition vs. Enzalutamide in Enzalutamide-Resistant In Vivo Mouse Model

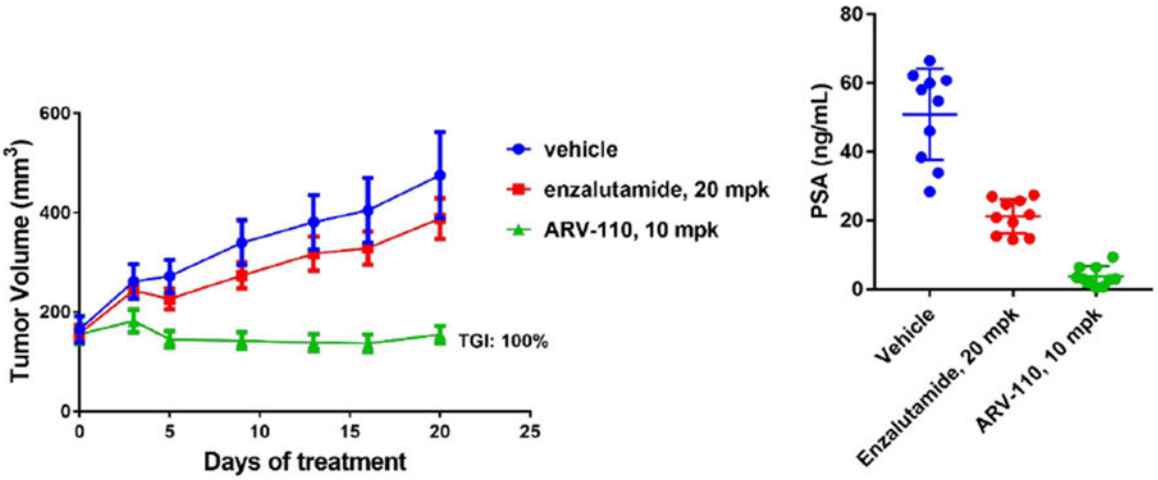


Abbreviations: AR=androgen receptor; hMito=human mitochondria; mpk=mg/kg; TGI=tumor growth inhibition; VCaP=vertebral cancer of the prostate (cell line).
Mice bearing enzalutamide-resistant VCaP xenograft tumors were dosed with enzalutamide or ARV-110 for 28 days. At the end of the study, the tumors were harvested 16 hours post last dose and the tumor AR, Erg, and FKBP5 (not shown) levels were established by western blotting. Antibody recognizing human mitochondria (Mito.C) was employed as a loading control. The quantitation of AR levels from the western blot is shown on the right.
Source: Study No. ARV-110-00011-00-INVIVO

Patient-Derived Xenograft Models

The effect of ARV-110 (10 mg/kg/day PO) and enzalutamide (20 mg/kg/day PO) was evaluated in a PDX model derived from a primary tumor located in the prostate gland of a [redacted]-year-old patient. A published report demonstrated no TGI in this model upon enzalutamide treatment, although modest PSA reductions were observed (Jin et al., 2017). The PDX was grown in intact (non-castrated) male NSG (NOD scid- IL2Rγ) mice. As shown in Figure 3, after 20 days of treatment, ARV-110 demonstrated 100% TGI, whereas no significant TGI was observed with enzalutamide. Plasma PSA levels were lowered following enzalutamide treatment (58% reduction), however, a 93% reduction of plasma PSA was observed with ARV-110 treatment. The difference between ARV-110 and enzalutamide PSA reduction was statistically significant (see IB for more information). These data demonstrate that ARV-110 is active in a prostate cancer PDX model that is largely insensitive to enzalutamide.

Figure 3. Efficacy of ARV-110 in Prostate Cancer PDX Mouse Model



Abbreviations: ELISA=enzyme-linked immunosorbent assay; mpk=mg/kg; PDX=patient-derived xenograft; PSA=prostate-specific antigen.
Tumor growth was measured twice weekly. At the termination of the experiment, the plasma PSA levels were measured with a PSA ELISA (Sigma).
Source: Study No. ARV-110-00074-00-INVIVO

4.2.2.3 Pharmacokinetics in Humans

The preliminary PK data from ongoing study ARV-110-mCRPC-101 in mCRPC patients are summarized in the IB including a summary table of PK data from 35 mg once daily (QD) to 700 mg QD and 140 mg twice daily (BID) to 420 mg BID.

Preliminary PK results indicated dose dependent increases in C_{max} and AUC for the specific enantiomers (ARCC-51A and ARCC-51B) and total ARV-110 on Day 15 or Day 21 (Day 15 or Day 21 time point depending on dose cohort) in each cohort up to 420 mg QD. At the 420 mg daily dose, the time to maximum plasma concentration (T_{max}) for total ARV-110 was achieved between 4- and 8-hours post-dose on Day 1 with the median T_{max} of 6 hours post-dose. Accumulation occurred between Day 1 and Day 15 or Day 21.

Exposure at 140 mg QD in humans with steady-state total ARV-110 AUC_{0-24} on Cycle 1 Day 15 has achieved the preclinical efficacious range associated with tumor growth inhibition in a VCaP tumor xenograft mouse model. In addition, exposure at 420 mg QD in human with steady-state total ARV-110 AUC_{0-24} on Cycle 1 Day 21 has achieved the preclinical efficacious range associated with tumor growth inhibition in an enzalutamide resistant VCaP tumor xenograft mouse model. Pharmacokinetic analysis is on-going, and updates will be provided in future versions of the ARV-110 IB.

4.2.2.4 Metabolism and Drug-Drug Interactions

In vitro assessment indicates CYP3A4 as the principal isoform responsible for ARV-110 CYP metabolism. Drugs that are inhibitors of CYP3A4 may increase the exposure of ARV-110, whereas drugs that are inducers of CYP3A4 may reduce the exposure of ARV-110.

ARV-110 is an in vitro inducer of CYP3A4 and an in vitro inhibitor of breast cancer resistance protein (BCRP) and P-glycoprotein (P-gp); these in vitro observations may need to be assessed further in the context of clinically relevant exposure/dose or investigated clinically, if necessary.

As a precaution, patients enrolled in the clinical trial are not allowed to receive drugs that are strong inducers/inhibitors of CYP3A4 or whose exposure may be altered by the induction of CYP3A4 or by the inhibition of BCRP and P-gp to a clinically significant extent.

Please see the ARV-110 IB for further information.

4.2.3 Abiraterone

Abiraterone is a structural analogue of pregnenolone, and inhibits CYP17, an enzyme necessary for the synthesis of androgens, including testosterone.

Abiraterone is approved by the FDA for the treatment of mCRPC and high-risk CSPC. Data for the approval in mCRPC come from large, randomized studies, that demonstrated abiraterone + prednisone improved overall survival (OS), progression-free survival (PFS), and time to PSA progression compared to placebo in patients in the pre- and post- chemotherapy setting (de Bono et al., 2011; Ryan et al., 2013). Data for the approval in CSPC comes from the double-blind, randomized Phase 3 clinical trial LATITUDE, which showed that ADT + abiraterone + prednisone improved rPFS and OS as compared to ADT + dual placebo in patients with newly diagnosed metastatic CSPC (Fizazi et al., 2017; Fizazi et al., 2019).

Since abiraterone can lead to adrenocortical insufficiency, steroids should be administered with abiraterone. Additionally, due to the mechanism of action of abiraterone, patients should be monitored for symptoms/signs of excess mineralocorticoids, especially in patients with cardiovascular disease.

The most common adverse reactions from abiraterone (≥10%) are fatigue, arthralgia, hypertension, nausea, vomiting, diarrhea, edema, hypokalemia, hot flushes, upper respiratory infection, cough, and headache (Abiraterone USPI, 2021). The most common laboratory abnormalities (≥20%) are anemia, elevated alkaline phosphatase (ALP), hypertriglyceridemia, hypercholesterolemia, hyperglycemia, hypokalemia, and lymphopenia (Abiraterone USPI, 2021).

Abiraterone is a substrate of CYP3A4, and an inhibitor of CYP2D6 and CYP2C8. It is recommended that patients avoid use of strong CYP3A4 inducers and CYP2D6 substrates that have a narrow therapeutic index. Additional information on abiraterone is available in the approved prescribing information.

4.3 BENEFIT/RISK ASSESSMENT

In patients with mPC who are having rising PSA values on abiraterone, adding ARV-110 may be of benefit.

Although second-generation AR antagonists and abiraterone have led to notable improvements in treatment of advanced/metastatic prostate cancer (Beer et al., 2014; de Bono et al., 2011; Ryan et al., 2013; Scher et al., 2012), a significant unmet medical need still exists since the majority of

patients become resistant to these agents after 6 to 15 months of treatment, and approximately 15% to 25% of patients do not respond to these agents as treatment for first-line mCRPC (Antonarakis, 2016; Arora et al., 2013; Beer et al., 2014).

Resistance to abiraterone may occur due to increased AR expression and continued AR activity from upregulation of steroid precursors (e.g., progesterone) or exogenous corticosteroids which can activate certain mutant forms of AR.

In this study, ARV-110 will be combined with abiraterone and administered to patients who are progressing on abiraterone to overcome resistance and achieve complete AR pathway blockade. Support for the combination of ARV-110 and abiraterone comes from preclinical data (ARV-110 IB and Section 4.2.2.1). In castrated mice bearing xenografts of the VCaP cell line, the combination of ARV-110 and abiraterone resulted in improved TGI compared to either agent alone. Furthermore, mice bearing abiraterone-resistant VCaP xenografts demonstrated TGI when treated with ARV-110. Additional rationale supporting the combination of ARV-110 and abiraterone (including data demonstrating improved efficacy of abiraterone plus apalutamide vs. abiraterone) are presented in Sections 4.2.1 and 6.4.

The combination of 420 mg of ARV-110 and abiraterone is expected to have a tolerable safety profile based on the side effect profile of abiraterone and available clinical data on ARV-110 from the ongoing FIH study (ARV-110-mCRPC-101) demonstrating tolerability up to doses of 630 mg daily. Additionally, data from clinical trials combining abiraterone with AR inhibitors (i.e., enzalutamide, apalutamide) suggest that dual targeting of the AR pathway can be performed in a safe manner.

Furthermore, ARV-110 may have advantages compared to the AR inhibitor enzalutamide, with preclinical data demonstrating that ARV-110 leads to TGI in enzalutamide-resistant xenograft models. Clinical data from the FIH study demonstrated evidence of early activity in 4 heavily pretreated patients with mCRPC achieving a PSA_{50} decline, 2 of whom had AR mutations known to lead to abiraterone resistance.

Potential overlapping toxicities for the combination of ARV-110 and abiraterone include fatigue, nausea, diarrhea, vomiting, and anemia. To minimize toxicity risk, all patients will be on stable doses of abiraterone prior to enrollment and have all adverse events (AEs) related to abiraterone reduced to ≤Grade 1. Guidance on the dose reduction of the study drugs is provided in Section 8.3.

Of note, in vitro data suggests ARV-110 induces CYP3A4, a key enzyme involved in the metabolism of abiraterone, and may consequently reduce abiraterone exposure. This potential drug-drug interaction (DDI) was considered in the design of this study, and early assessments of the abiraterone PK profiles will be used to adjust the dose of abiraterone if needed.

5. OBJECTIVES AND ENDPOINTS

Table 6. Objectives and Endpoints

Objective	Endpoint
Primary	
Evaluate the safety and tolerability of ARV-110 in combination with abiraterone and select the RP2D/ schedule for the combination.	The following safety endpoints will be assessed: • Dose-limiting toxicities (DLTs) in first 4 weeks of the study combination treatment and determination of the RP2D • AEs as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), timing, seriousness, and relationship to study drug combination • Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), and timing
Secondary	
Characterize the PK of abiraterone when given alone and in combination with ARV-110. Characterize the PK of ARV-110, when given in combination with abiraterone.	The following PK parameters of abiraterone and ARV-110, will be assessed if data allows: AUC_{tau}, AUC_{last}, C_{max}, C_{min}, T_{max}, C_{last}, T_{last}. See Table 12 for definitions.
Assess preliminary antitumor activity.	Antitumor activity of ARV-110 in combination with abiraterone will be assessed by evaluating the following: • Percent of patients with lack of PSA progression • PSA30 and PSA50 response rate and duration • Time to PSA progression • rPFS • ORR per modified RECIST 1.1/PCWG3 and DOR in patients with measurable disease at baseline
Exploratory	
[redacted]	

Abbreviations: AE=adverse event; AR=androgen receptor; [redacted]; CTCAE=Common Toxicity Criteria for Adverse Events; [redacted] DOR=duration of response; NCI=National Cancer Institute; ORR=overall response rate; PCWG3=Prostate Cancer Working Group 3; PK=pharmacokinetic(s); PSA=prostate-specific antigen; $PSA_{30,50}$=a >30% or ≥50% decline in PSA from Cycle 1 Day 1 (baseline) PSA value; RECIST=Response Evaluation Criteria in Solid Tumors; RP2D=recommended Phase 2 dose; rPFS=radiographic progression-free survival.

6. STUDY DESIGN

6.1 OVERALL DESIGN

The study is an open-label, multicenter, non-randomized study of ARV-110 in combination with abiraterone and a concomitant corticosteroid. The study is designed to assess the safety, PK, and preliminary clinical activity of the combination in patients with mPC who have rising PSAs (without known radiographic disease progression), while receiving abiraterone with a

concomitant corticosteroid. The study design has accounted for potential DDIs between ARV-110 and abiraterone, which may reduce abiraterone exposure.

Approximately 40 patients will be treated on this study, with an initial safety lead-in consisting of 3-6 dose-limiting toxicity (DLT)-evaluable patients. All patients in the initial safety lead-in will receive ARV-110 420 mg PO daily, and will continue abiraterone and a corticosteroid PO daily (at the same doses they were previously receiving as standard of care).

A Safety Review Committee (SRC) will examine all available data from the safety lead-in to determine the RP2D and before additional patients can be treated. The tolerability and dose justification of ARV-110 in the combination for the safety lead-in will be determined by Bayesian Optimal Interval Design (BOIN) modeling (Yuan et al., 2016) with a target DLT rate of 30% (see Table 7).

After SRC evaluation of the 3-6 patient safety lead-in:

- If the DLT rate is acceptable (<0.358), enrollment will continue until a total of approximately 40 patients are treated. If abiraterone exposure reduces by approximately 50% or more in the safety lead-in, the frequency of abiraterone administration may be increased to BID based on SRC recommendation. The decision to increase the frequency of abiraterone will be based on available PK and safety data.
- If the DLT rate is not acceptable (≥0.358), the safety lead-in will be repeated with an additional 3-6 DLT-evaluable patients. The dose of ARV-110 or abiraterone may be reduced per SRC recommendations. The dose of ARV-110 may be reduced to 280 mg or 140 mg daily. The dose of abiraterone may be reduced to 750 mg or 500 mg daily.

Table 7. Dose Adjustment Rules Based on Observed Dose-Limiting Toxicity Rate

Observed DLT Rate and Examples	Decision Rule on Dose Adjustment per BOIN Modeling
DLT rate <0.358 *	No dose de-escalation (abiraterone dose may be increased from daily to BID based on safety and PK data per SRC recommendation)
N=3,4, or 5; number of DLTs less than 2	
N=6; number of DLTs less than 3	
DLT rate ≥0.358	Dose de-escalation of ARV-110 or abiraterone per SRC recommendation
N=3,4, or 5; number of DLTs ≥2	
N=6; number of DLTs ≥3	

Abbreviations: BID=twice daily; BOIN=Bayesian Optimal Interval Design; DLT=dose-limiting toxicity; PK=pharmacokinetic(s); SRC=Safety Review Committee.
* A prespecified dose de-escalation boundary DLT rate of 0.358 was chosen per BOIN modeling based on the target DLT rate of 30%.

Ongoing safety reviews will be performed by the SRC throughout the conduct of the study as outlined in Section 12. Intensive PK sampling will be performed on all patients in the safety lead-in as outlined in Table 3. Intensive PK sampling may also be performed on patients outside of a safety lead-in based on SRC recommendation.

Patients may remain on study until progression of disease by modified Response Evaluation Criteria in Solid Tumors (RECIST) 1.1/ Prostate Cancer Working Group 3 (PCWG3) criteria, the occurrence of a treatment-emergent adverse event (TEAE) warranting discontinuation, or withdrawal of patient consent.

Screening Phase

Screening begins by establishing the patient's initial eligibility and signing of the informed consent form (ICF) and registration in the interactive response technology (IRT) system to obtain the Patient ID number. Screening tests are listed in the Schedule of Activities (SoA; Section 3).

The Screening phase ends with either confirmation of full eligibility and enrollment for the patient or with the confirmation that the patient is a screen failure.

Treatment Phase

The Treatment Phase begins when the patient is enrolled for treatment in the IRT system.

Patients may continue treatment until disease progression, the occurrence of a TEAE warranting discontinuation, death, withdrawal of patient consent, or when patients meet other study treatment-stopping criteria (see Sections 8.3.6 and 9.1).

Patients who have evidence of radiographic disease progression may be considered for continued study drug treatment provided the Investigator has determined that they are still benefiting from study drug (e.g., improvement of cancer-related symptoms). All such requests must be discussed with and approved by the Arvinas Medical Monitor.

The Treatment phase ends when the patient is discontinued from all study drug treatment.

Follow-up Phase

An End of Treatment (EOT) and Follow-up visit will be performed following treatment discontinuation.

The EOT visit is to be performed as soon as possible, but no later than 4 weeks, from the last dose of study drug and prior to initiation of any new antitumor therapy. Required assessments not completed during the previous 4 weeks on study will be obtained at the EOT visit. Clinical laboratory assessments, physical examinations, and AE assessments will be performed at the EOT visit. Any TEAEs that are ongoing will be assessed at this visit and at the Follow-up visit that will take place 28 to 35 days after treatment discontinuation. Patients continuing to experience treatment-related toxicity at the time of the Follow-up visit will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the Investigator, that no further improvement is expected.

6.2 DOSE-LIMITING TOXICITIES

Patients will be considered DLT evaluable if:

a) They received the combination ARV-110 and abiraterone for at least 22 days (80% of the doses)

OR

b) They received at least 1 day of combination of ARV-110 and abiraterone, and had a DLT within 28 days of starting the ARV-110 and abiraterone combination.

Patients who only receive abiraterone will not be considered DLT evaluable. Patients who fail to complete at least 80% of study drug treatment in Cycle 1 for reasons other than DLT (e.g., logistical or technical reasons, non-DLT-related dose delays) are considered not to be DLT evaluable. Any patients in safety lead-in that are not DLT evaluable may be replaced, but they can remain on study and continue to receive treatment.

Patients with AEs that are attributable to ARV-110 or abiraterone, and unrelated to mPC, intercurrent illness, or concomitant medications will be classified as DLT evaluable.

The severity of AEs will be graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. All TRAEs of the specified grades below should count as DLTs except those that are clearly and incontrovertibly due to disease progression or extraneous causes.

Hematologic DLTs

- Prolonged myelosuppression, defined as CTCAE Grade ≥3 hematologic parameters (absolute neutrophil count [ANC] <1000/mm^3, platelet count <50,000/mm^3, or hemoglobin [Hgb] <8 g/dL) in a bone marrow with <5% blasts and no evidence of leukemia or abnormal dysplasia, that lasts longer than 28 days from the point of detection.
- Grade ≥3 neutropenia with infection.
- Grade 4 neutropenia lasting >5 days.
- Febrile neutropenia (defined as an ANC <1.0×10^9/L with a single temperature of >38.3°C or 101°F, or a sustained temperature of ≥38°C or 100.4°F for more than 1 hour).
- Grade 3 thrombocytopenia with clinically significant bleeding.
- Grade 4 thrombocytopenia.
- Any toxicity requiring dose interruption for ≥14 days will be considered a DLT.

Non-Hematologic DLTs

- Grade ≥3 toxicities that are considered clinically significant.
- Non-clinically significant Grade ≥3 toxicities requiring dose interruption for ≥10 days that are determined by the Investigator to be clinically relevant may be deemed a DLT after review by the SRC.
- In cases of ≥Grade 3 amylase not associated with symptoms or clinical manifestations, radiological imaging should be performed.
- Dose delay >5 days due to a TRAE.
    - Concomitant alanine aminotransferase (ALT) or AST elevation of >3× upper limit of normal (ULN) and total bilirubin ≥elevation of >2× ULN without a clear alternative etiology.
    - Corrected QT interval by Fridericia's method (QTcF) prolongation: In an asymptomatic patient, Grade 3 QTcF prolongation (QTcF >500 msec) will first require repeat testing, re-evaluation by qualified personnel, and correction of reversible causes such as electrolyte abnormalities or hypoxia for confirmation. If, after correction of any reversible causes, the Grade 3 QTcF prolongation persists, then the event should be considered a DLT.
- Any toxicity requiring dose interruption for ≥14 days will be considered a DLT.

Clinically important or persistent toxicities (e.g., toxicities responsible for significant dose delay) that are not included in the above criteria may also be considered a DLT following review by the Investigators and the Sponsor. To be considered a DLT, the AE must represent a clinically significant shift from baseline and must be considered at least likely related to ARV-110 by the Investigator or Sponsor.

Non-Hematologic AEs that are NOT Considered DLTs

- Grade 3 nausea/vomiting/diarrhea lasting <72 hours with adequate anti-emetic and other supportive care are NOT considered a DLT.
- Grade 3 fatigue lasting less than 7 days is NOT considered a DLT.

6.3 NUMBER OF PATIENTS

Approximately 40 patients are expected to be treated on the trial.

6.4 END OF STUDY DEFINITION

The start of the trial is defined as the first patient's first visit. End of study is defined as the last patient's last study visit or phone call. Study completion is defined as the final date on which data for the primary endpoint was or is expected to be collected if this is not the same.

For patients on treatment after primary study completion, see Table 5, Section 6.7, and Appendix 10.

6.5 RATIONALE FOR SELECTION OF PATIENTS

This study will examine the combination of ARV-110 and abiraterone in patients with mPC who have rising PSAs on abiraterone. Despite available treatment options, when patients progress on abiraterone, their responses to enzalutamide and chemotherapy are significantly lower than in the abiraterone-naïve setting.

This study will exclude patients who have received prior second-generation AR inhibitors (e.g., enzalutamide, apalutamide). Over the course of treatment from hormone-sensitive to castration-resistant disease, prostate cancer growth can lose dependence on AR and accumulate mutations in a variety of genes including the tumor suppressors TP53, RB1, and PTEN. Therefore, ARV-110 may have improved antitumor activity in patients treated with fewer lines of prior therapy, as they are more likely to be dependent on the AR signaling axis for growth.

6.6 RATIONALE FOR DOSE

Based on data from the FIH study in mCRPC, ARV-110-mCRPC-101, a dose of 420 mg PO QD was selected for this this study. The 420 mg QD dose was well-tolerated and resulted in average exposures above the predicted efficacy thresholds based on enzalutamide-resistant CRPC model.

Exposure at 420 mg QD in humans with steady-state total ARV-110 AUC_{0-24} on Cycle 1 Day 21 has achieved the preclinical efficacious range associated with tumor growth inhibition in an enzalutamide resistant VCaP tumor xenograft mouse model.

Abiraterone is a substrate of CYP3A4. Based on in vitro data, ARV-110 is an inducer of CYP3A4 and may lead to decreased abiraterone exposure. Patients will continue on same dose of abiraterone they were on prior to study enrollment. Data from the safety lead-in will be reviewed by the SRC, and if abiraterone exposure reduces by approximately 50% or more, the frequency of abiraterone administration may be increased to BID. The decision to increase the frequency of abiraterone will be based on the totality of available PK and safety data.

Dose reduction of both ARV-110 and abiraterone will be permitted as per Section 8.3.

6.7 RATIONALE FOR PATIENTS CONTINUING ON TREATMENT AFTER NOTICE FROM SPONSOR OF PRIMARY STUDY COMPLETION

The primary purpose of this amendment is to provide guidance for patients who continue to receive study treatment after the primary study completion date. This date will be at least 9 months after the last patient first visit, which allows for evaluation of the key study objectives (i.e., safety, tolerability, PK, and efficacy). This amendment provides instructions for a modified patient visit schedule with reduced data collection.

After the notice of primary study completion, the clinical study database will close to collection of new data. Patients are, however, permitted to continue to receive study treatment beyond the closure of the database if, in the opinion of the Investigator, they are continuing to receive benefit from the study treatment. Investigator will continue to refer to the protocol and follow the SoA as described in Table 5.

For patients who do continue to receive treatment beyond the time of this data cut-off, Investigators will continue to report all SAEs, AEs leading to discontinuation of study drug, and deaths due to disease progression via the paper reporting mechanism detailed in Section 10.2.1.1 and Appendix 5. Clinical data generated from new patient visits will continue to be collected in site source but will not be entered into the clinical electronic database electronic case report form (eCRF). Additionally, as stated in Table 5, patients continuing to experience treatment-related toxicity at the time of EOT, will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the Investigator, that no further improvement is expected. The investigator will continue to refer to the protocol, and notify the Sponsor, when necessary, as per the protocol (e.g., intolerable AEs, dose modification).

7. STUDY POPULATION

Eligibility criteria for this study have been carefully considered to ensure the safety of the study patients. It is imperative that patients fully meet **all** eligibility criteria.

7.1 INCLUSION CRITERIA

To be considered eligible to participate in this study, all of the following requirements must be met:

a. Informed Consent

1. Patients must have signed and dated an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written ICF in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol related procedures that are not part of normal patient care.
2. Patients must be able and willing to conform with visit and treatment schedule and laboratory procedures.
3. Patients must be able to take oral medication without crushing, dissolving, or chewing tablets/capsules.

b. Patient Disease Characteristics

4. Histological, pathological, or cytological confirmed diagnosis of adenocarcinoma of the prostate.
5. Ongoing treatment with stable doses of abiraterone (on an empty stomach) and a concomitant corticosteroid for mCRPC or for mCSPC until C1D1. If a patient had treatment interruptions or dose modifications of abiraterone within 2 weeks of C1D1, the Investigator must inform the Medical Monitor (or designee).
6. Recent PSA values must demonstrate:
    a. Rising PSAs at least 16 weeks after initiation of abiraterone; and
    b. At least 2 PSA values that are higher than the PSA nadir on abiraterone, measured at a minimum of 1 week apart. The screening PSA for this study may be used as the 2nd PSA value.

7. No known radiographic evidence of disease progression while receiving abiraterone and clinically benefitting at the time of consent. If there is evidence of radiographic disease progression during screening, the patient may be considered eligible if, in the judgement of the investigator, the patient is clinically benefitting from abiraterone.
8. Ongoing ADT with a gonadotropin-releasing hormone (GnRH) analogue or inhibitor, or orchiectomy (surgical or medical castration).
9. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (Appendix 8).
10. The following PSA values with dates must be documented in an electronic case report form (eCRF) for all patients:
    - Last PSA prior to initiation of abiraterone
    - PSA nadir while on abiraterone
    - Rising PSAs at least 16 weeks after initiation of abiraterone (including 2 PSA values at least 1 week apart; the screening PSA for this study may be used as the 2nd PSA value)

c. Physical and Laboratory Findings

11. Adequate bone marrow function defined as follows (with no transfusion of blood products or use of hematopoietic growth factors in the 28 days prior to enrollment):
    - Absolute neutrophil count $\geq 1500/mm^3$ or $\geq 1.5 \times 10^9/L$
    - Platelets $\geq 100{,}000/mm^3$ or $\geq 100 \times 10^9/L$
    - Hemoglobin ≥ 9 g/dL
12. Adequate renal function defined as an estimated creatinine clearance of ≥ 50 mL/min.
13. Adequate liver function defined as:
    - Total serum bilirubin $\leq 1.5\times$ ULN
    - AST and ALT of $\leq 2.5\times$ ULN if there is no liver involvement secondary to tumor, or $\leq 5.0\times$ ULN if there is liver involvement secondary to tumor
14. Adverse reactions of any prior therapy (including abiraterone) have resolved to baseline severity or Grade ≤ 1 by NCI CTCAE except for the following:
    - alopecia
    - peripheral neuropathy

d. Age and Reproductive Status

15. Males ≥18 years of age, inclusive, at the time of signing the ICF.
16. Males who are sexually active must agree to use contraception (unless confirmed prior castration) as detailed in Appendix 6 of this protocol during the treatment period and for at least 16 weeks after the last dose of study treatment and refrain from donating sperm for at least 16 weeks after the last dose of study drug.

Investigators shall counsel male patients who are sexually active with women of childbearing potential (WOCBP) on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise on the use of highly effective methods of contraception (Appendix 6) that have a failure rate of <1% when used consistently and correctly.

7.2 EXCLUSION CRITERIA

Patients will **not** be eligible for this study if any of the following criteria are met:

e. Prior or Concomitant Treatments

1. Previously treated with enzalutamide, apalutamide, darolutamide, or experimental therapies (e.g., protein degraders or inhibitors) directed at the AR.
2. Treatment with any chemotherapy, investigational agents, immunotherapy, or hormonal therapy other than GnRH agonists within 28 days of the start of treatment on protocol.
3. Radiation therapy within 4 weeks of first dose of study drug or prior irradiation to >25% of the bone marrow. Palliative radiation for the alleviation of pain due to bone metastasis will be allowed during the study.
4. Patients taking agents that are either a) sensitive P-gp, BCRP, or CYP3A4 substrates, b) P-gp, BCRP, CYP3A4, or CYP2D6 substrates that have a narrow therapeutic index, c) strong CYP3A4 inhibitors or inducers, or d) any other prohibited and/or restricted medications described in Section 8.7.2.
5. Major surgery (as judged by the Investigator) within 4 weeks of first dose of study drug.

f. Medical Conditions

6. Untreated brain metastases or brain metastases requiring steroids above physiologic replacement doses. Patients with previously diagnosed brain metastases are eligible if they have completed definitive treatment and have recovered from the acute effects of radiation therapy or surgery prior to first dose of study drug, have discontinued high-dose corticosteroid treatment for these metastases for at least 4 weeks prior to C1D1, and are neurologically stable as judged by the Investigator.
7. Any other active malignancy within 3 years prior to enrollment, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ. Other localized malignancies considered highly curable by the Investigator are eligible.

8. Any of the following in the previous 12 months: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure (New York Heart Association class II, III or IV), cerebrovascular accident, transient ischemic attack, symptomatic pulmonary embolism, or other clinically significant episode of thromboembolic disease.
9. Any of the following in the previous 6 months: congenital long QT syndrome, Torsade de Pointes, arrhythmias (including sustained ventricular tachyarrhythmia and ventricular fibrillation), left anterior hemiblock (bifascicular block), or ongoing cardiac dysrhythmias of NCI CTCAE Grade ≥2, atrial fibrillation of any grade (Grade ≥2 in the case of asymptomatic lone atrial fibrillation).
10. Hypertension that cannot be controlled by medications (>150/90 mmHg despite optimal medical therapy).
11. Active, uncontrolled bacterial, fungal, or viral infection, including hepatitis B virus, hepatitis C virus, known human immunodeficiency virus (HIV), or acquired immune deficiency syndrome (AIDS)-related illness. Patients whose viral load is negative or HIV-seropositive patients who are healthy and low risk for AIDS-related outcomes may be considered eligible. HIV-positive patients should be free of any serious AIDS defining conditions (e.g., opportunistic infections) with an undetectable viral load.
12. Active inflammatory gastrointestinal disease, uncontrolled chronic diarrhea, known diverticular disease, or previous gastric resection or lap band surgery. Gastroesophageal reflux disease is allowed provided that treatment with prohibited medications (e.g., proton pump inhibitors) is not required.
13. Patients with Child Pugh C.
14. Patients with electrolyte imbalances of hypokalemia, hypomagnesemia, and/or hypocalcemia.
15. Patients with QTcF ≥470 msec.

g. Allergy and Other Drug Reactions

16. Suspected hypersensitivity to ARV-110.
17. History of allergy or reaction to any of the drug components.

h. Other Exclusion Criteria

18. Other acute or chronic severe medical or psychiatric condition, including recent (within the past year) or active suicidal ideation or behavior, or laboratory abnormality that may increase the risk associated with study participation or study drug administration or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the patient inappropriate for entry into this study.

7.3 LIFESTYLE RESTRICTIONS

Restrictions regarding lifestyle, activities, and/or diet required for study eligibility and/or participation are listed below. Patients will be instructed by the study staff on the following:

- Patients will take ARV-110 orally as described in Section 8.2.
- Patients need to apply sunscreen products and avoid excessive sun exposure during study drug treatment.

7.4 SCREEN FAILURES

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently enrolled. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and to respond to queries from regulatory authorities. Minimal information includes date of consent, demography, screen failure details, eligibility criteria, and any serious AEs.

Individuals who do not meet the criteria for participation in this study (screen failures) need to be indicated as such in the IRT, or may be rescreened once. Rescreened patients should not be assigned the same patient number as the one they received in the initial screening.

7.4.1 Retesting During Screening

Retesting of laboratory parameters and/or other assessments within the Screening period will be permitted (in addition to any parameters that require a confirmatory value).

The most current result prior to enrollment is the value by which study inclusion will be assessed, as it represents the patient's most current, clinical state.

8. TREATMENT

8.1 PRODUCT DESCRIPTION

In this study, the following is considered an active investigational product/investigational medicinal product (IP/IMP): ARV-110 and abiraterone; see Table 8.

Table 8. Product Descriptions

Product Description and Dosage Form	Unit Dose Strengths	Primary Packaging	Appearance	Route of Administration
ARV-110 Tablets	140 mg	High-density polyethylene bottle	Light yellow to yellow, round tablet	Oral
Abiraterone Tablets	500 mg	See Pharmacy Manual for full descriptions and Section 8.4		Oral
Abiraterone Tablets	250 mg			Oral
The Pharmacy Manual contains all relevant study drug treatment instructions and information.				

A concomitant corticosteroid of the Investigator's choice will be administered with abiraterone according to recommended local practice guidelines and package label inserts.

Study Drug Packaging and Labeling: The label text of the study treatment supplies will comply with Good Manufacturing Practice (GMP) and national legislation to meet the requirements of the participating sites/countries (see Section 8.4).

Study Drug Storage: All study treatment supplies must be stored in accordance with the study-specific Pharmacy Manual instructions and package labeling. Until dispensed or administered to the patients, the study drugs will be stored in a securely locked area that is accessible only to authorized personnel (see Section 8.4).

Other medications used as support for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as non-investigational products.

8.2 TREATMENTS ADMINISTERED

The prescribed dosage, timing, and mode of administration may not be changed, except as defined in Section 8.3. Any departures from the intended regimen must be recorded in the eCRFs.

All patients will receive abiraterone and ARV-110 as per Table 9. ARV-110 is an in vitro inducer of CYP3A4 and abiraterone is a CYP3A4 substrate and as such abiraterone exposure may be reduced when given with ARV-110. Cycle 1 PK data from the patients in the safety lead-in will determine the impact, if any, of ARV-110 on reducing the level of abiraterone via CYP3A4 induction. Based on the results of the safety lead-in, the dose of abiraterone or ARV-110 may be adjusted as appropriate for patients already on trial as well as the newly enrolled patients.

Table 9. Study Drugs Administered

ARV-110 Dose	Abiraterone Dose	ARV-110 and Abiraterone IMP Start Day
420 mg daily [1]	The last dose of abiraterone that the patient was receiving prior to study enrollment (1000 mg daily or less) [1,2]	C1D1

Abbreviations: BID=twice daily; C1D1=Cycle 1, Day 1; DLT=dose-limiting toxicity; SRC=Safety Review Committee.

1 If the DLT rate in the safety lead-in is not acceptable (≥0.358), the dose of ARV-110 or abiraterone may be reduced per SRC recommendations. The dose of ARV-110 may be reduced to 280 mg or 140 mg daily. The dose of abiraterone may be reduced to 750 mg or 500 mg daily.

2 If the DLT rate in the safety lead-in is acceptable (<0.358) and abiraterone exposure reduces by approximately 50% or more, the frequency of abiraterone administration may be increased to BID based on SRC recommendation.

All patients will receive 140-mg tablets of ARV-110, and either 500-mg or 250-mg tablets of abiraterone.

Patients will take abiraterone QD (at the same dose they were on prior to study enrollment), beginning at C1D1 on an empty stomach (at least 1 hour before or 2 hours after meal), with a concomitant corticosteroid of Investigator's choice as per local label/guidelines.

Patients will also take ARV-110 at 420 mg by mouth QD with food (meal of ≥400 calories that includes a mixture of fat, carbohydrates, and protein). It is recommended that patients take ARV-110 with the largest meal of the day (e.g., dinner), except for days when PK sampling is performed in the clinic. ARV-110 tablets are to be swallowed whole and must not be crushed, chewed, or dissolved. Taking ARV-110 with adequate food is important, and patients should be instructed of this.

Patients will self-dose, except for days when PK sampling is performed. PK sampling is performed on Day -1 (-7 day window), and at various timepoints starting on C1D1. On PK sampling days, patients should be instructed not to take abiraterone or ARV-110 at home as the dose will be administered at the clinic. In addition, they should be instructed that they will be provided with food in the clinic that is to be eaten prior to taking the study drug ARV-110, and therefore should refrain from eating or have a light snack prior to their clinic appointment time. While in clinic, patients will take abiraterone first on an empty stomach, and at least 1 hour later, take ARV-110 with food.

Patients should take the ARV-110 dose at approximately the same time every day. A missed dose can be taken later in the day providing it is at least 12 hours prior to the next scheduled dose. Otherwise, the patient should skip the dose and proceed with the next planned dose the following day. Patients should not double up on doses to make up for missed doses. Patients should record any missed doses in their dosing diary.

Please see Table 3 and Table 4 for detailed instructions on sequencing the study drugs on days when PK samples are collected.

8.2.1 Method of Treatment Assignment

All patients will be registered using an IRT system. Study site users will receive log-in information and directions on how to access the IRT system. Specific instructions for using the IRT will be provided to the investigational site in a separate document.

Following the signing of informed consent, investigative staff will enroll the patient in the IRT system to obtain the patient ID number. Enrolled patients that have met all eligibility criteria will have eligibility confirmed in the IRT system prior to the start of study treatment. Enrolled patients that fail to meet 1 or more eligibility criteria will be indicated as screen fail in the IRT system.

8.2.1.1 Method of Treatment Dispensation for Patients on Treatment After Notice From Sponsor of Primary Study Completion

Following the notice from Sponsor of primary study completion, notification of database lock, and IRT closure from Sponsor, for patients who are continuing study treatment, sites will receive study drug via manual drug resupply system. Refer to updated Pharmacy Manual for details.

8.3 TREATMENT MODIFICATIONS AND DISCONTINUATIONS

Dosing modifications for both ARV-110 and abiraterone as well as dose interruptions and criteria to resume or discontinue treatment are discussed in this section.

Notify the Sponsor of any treatment-related intolerable Grade 2 or any Grade ≥3 events.

a. For toxicity requiring withholding of 1 study drug, both study drugs should be held until the AE returns to Grade ≤1 or baseline.

b. For toxicity that is clearly attributable to abiraterone and requires permanent discontinuation of abiraterone, ARV-110 may be continued after discussion with the Medical Monitor.

c. For toxicity that is clearly attributable to ARV-110 and requires permanent discontinuation of ARV-110, abiraterone must also be permanently discontinued.

8.3.1 Dose Modifications for QTc Prolongation (Regardless of Causality)

In the event of QTcF prolongation (regardless of causality), possible alternate reversible causes (e.g., electrolytes, concomitant medications) should be evaluated. If reversible causes are identified, they should be corrected accordingly. If reversible causes are not identified, dose adjustments may be required as described below.

- Grade 1: no dose adjustments or additional monitoring is required.
- Grade 2: no dose adjustments are required. If the QTcF remains above 480 msec for more than 2 cycles or if Grade 2 QTcF prolongation recurs in the absence of other alternative causes or despite correction of alternative causes, dose adjustment and/or discontinuation should be considered in consultation with a cardiologist and the study medical monitor, taking into account the emerging safety data from ARV-110 trials and the Investigator's best medical judgment. Initiate more frequent ECG monitoring per Investigator's judgement until QTcF ≤480 msec or ≤60 msec change from baseline.
- Grade 3: withhold *both* ARV-110 and abiraterone treatment until Grade ≤2. If an alternate reversible cause is identified, resume treatment at the same dose level. If a reversible cause is not identified, reduce ARV-110 by 1 dose level per Table 10. Initiate more frequent ECG monitoring per Investigator judgement until QTcF ≤480 msec or ≤60 msec change from baseline.

Grade 4: permanently discontinue all study treatment

8.3.2 Dosage Modifications for ARV-110 Treatment-Related AEs

For all Grade 3 or intolerable Grade 2 AEs related to ARV-110, patients should hold both ARV-110 and abiraterone until the AE returns to Grade ≤1 or baseline. The study drug may be resumed using guidelines in Table 10.

Of note, AST/ALT elevations or hepatotoxicity may occur due to DDIs involving ARV-110. For AST/ALT increase that is likely attributed to a DDI, **both drugs** involved in the interaction must be held. Dose modification of ARV-110 must be discussed with the Medical Monitor and may not be necessary if the other offending agent has been discontinued.

Table 10. Dose Reduction – Guidance for ARV-110 Treatment-Related AEs

AE	ARV-110 Dose Modification
Related Non-Hematologic Grade 3 or Intolerable Grade 2 AE [a]	
First Dose Reduction [b]	Reduce to 280 mg daily
Second Dose Reduction	Reduce to 140 mg daily **(except second occurrence of AST/ALT increase requires permanent discontinuation)**
Third Dose Reduction	Discontinue ARV-110 [c]
Related Grade 3 Hematologic AEs >7 days [d]	
First Dose Reduction	Reduce to 280 mg daily **(except thrombocytopenia associated with bleeding and neutropenic fever require permanent discontinuation regardless of AE duration)**
Second Dose Reduction	Reduce to 140 mg daily
Third Dose Reduction	Discontinue ARV-110 [c]
Related Non-Hematologic Grade 4 AE [e]	Discontinue ARV-110
Related Hematologic Grade 4 AE	
First Dose Reduction	Reduce to 280 mg daily **(except thrombocytopenia, neutropenia >5 days, and neutropenic fever require permanent discontinuation)**
Second Dose Reduction	Reduce to 140 mg daily
Third Dose Reduction	Discontinue ARV-110 [c]

Abbreviations: AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; DDI=drug-drug interaction.

Note: Depending on the nature of the AEs, a more conservative dose reduction could be considered after discussion with the Medical Monitor.

a. Grade 3 AEs not requiring dose reductions: Grade 3 fatigue lasting less than 7 days; Grade 3 nausea/vomiting/diarrhea lasting less than 72 hours in the absence of maximal medical therapy.
b. For AST/ALT increase that is clearly attributed to a DDI, both drugs involved in the interaction must held (ARV-110 and the other offending drug). Dose modification of ARV-110 must be discussed with the Medical Monitor and may not be necessary if the other offending agent has been discontinued.
c. If the patient has demonstrated significant benefit, the AE was rapidly reversible, and redosing is not expected to pose a significant risk to the patient, resumption of ARV-110 without dose reduction may be considered dependent on the nature of the AE after consultation with the Medical Monitor.
d. Grade 3 AEs not requiring dose reductions: Grade 3 anemia of any duration not requiring transfusion; isolated Grade 3 reduction in eosinophils, basophils, or lymphocytes of any duration.
e. Grade 4 AEs not requiring discontinuation: Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset. Dose modification of ARV-110 must be discussed with the Medical Monitor.

8.3.3 Dose Modifications for Abiraterone:

Dose modification guidelines for dose reduction of abiraterone in the setting of hepatotoxicity are provided in table below (as per Abiraterone USPI, 2021). AST/ALT increase may be caused by either ARV-110 or abiraterone. If the AST/ALT increase (or hepatotoxicity) is attributed to ARV-110 only (e.g., due to a DDI), abiraterone dose does not need to be modified.

For all other AEs considered related or potentially related to abiraterone, the Medical Monitor must be contacted if the Investigator is considering abiraterone dose reduction.

If a more recent locally approved abiraterone label is available, those guidelines will supersede the guidelines provided below.

Liver Function Test (LFT) Increase Related to Abiraterone	Abiraterone Dose Modification
First Occurrence (on 1000 mg QD): AST/ALT >5× ULN or Total bilirubin (Tbil) >3× ULN	• Interrupt treatment • Restart treatment at 750 mg once daily when LFTs return to baseline or • AST/ALT ≤2.5× ULN and Tbil ≤1.5× ULN • Monitor AST/ALT/bilirubin at least every 2 weeks for 3 months, and then monthly thereafter
Second Occurrence (on 750 mg QD): AST/ALT >5× ULN or Tbil >3× ULN	• Interrupt treatment • Restart treatment at 500 mg QD when LFTs return to baseline or • AST/ALT ≤2.5× ULN and Tbil ≤1.5× ULN • Monitor AST/ALT/bilirubin at least every 2 weeks for 3 months, and then monthly thereafter
Third Occurrence (on 500 mg QD): AST/ALT >5× ULN or Tbil >3× ULN	• Discontinue abiraterone and ARV-110
ALT >3× ULN **and** Tbil >2× ULN	• Discontinue abiraterone and ARV-110

8.3.4 Dose Interruption Criteria for Study Treatment

Dosing for any individual patient may be interrupted (i.e., treatment may be temporarily held) if the patient experiences an AE that, in the opinion of the Investigator or Sponsor's medical representative, warrants a dose interruption for that patient's wellbeing. In such cases, regardless of whether the AE is related to ARV-110 and/or abiraterone, both study drugs must be held until criteria to resume treatment (Section 8.3.5) have been met. The Medical Monitor should be notified when a decision is made to interrupt or hold study drug.

Study drug administration should be interrupted for any of the following:

- Grade 2 or 3 AST and/or ALT elevation.
- Any other non-hematologic Grade 3 or intolerable Grade 2 event.

Patients who require interruption of study drug should be re-evaluated weekly or more frequently if clinically indicated and resume study drug dosing when retreatment criteria are met. If a patient's treatment is interrupted more than 28 days due to a TRAE, study drug treatment will be permanently discontinued (see Section 8.3.6).

Tumor assessment(s) for the patient should continue as per protocol even if dosing is interrupted.

A positive COVID-19 test will not require a dose interruption. In such cases any dose interruption should be based on the severity of any associated symptoms, the need for COVID-19 treatment, and the Investigator's judgment or patient's request. If dosing is interrupted, dosing may resume without dose modification and based on Investigator's judgment. The Medical Monitor or Designee should be notified if treatment of COVID-19 is needed or there is prolonged treatment interruption due to COVID-19. See Appendix 9.

8.3.5 Criteria to Resume Treatment

Patients may resume treatment with study drug when the AE(s) resolve to Grade ≤1 or baseline value within 28 days of initially interrupting treatment.

The following are exceptions to the above:

- Patients may resume treatment in the presence of Grade 2 fatigue.
- Dosing interruptions >28 days that occur for non-treatment-related reasons may be allowed if approved by the Sponsor. Treating physicians must discuss with the Medical Monitor prior to re-initiating study drug therapy.

8.3.6 Treatment Discontinuation Criteria

Dosing for any individual patient may be stopped if the patient experiences a possible treatment-related DLT or a clinically significant study TRAE that in the opinion of the Principal Investigator, or Sponsor's medical representative, warrants discontinuation of the study for that patient's wellbeing.

A patient may withdraw from the study at any time at his own request or may be withdrawn from study treatment at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons (see Section 9.1).

Treatment should be permanently discontinued for any of the following:

- Any AE meeting criteria for permanent discontinuation of ARV-110 or abiraterone as described in Sections 8.3.1 and 8.3.3. For toxicity that is clearly attributable to abiraterone and requires permanent discontinuation of abiraterone, ARV-110 may be continued after discussion with the Medical Monitor. -For toxicity that is clearly attributable to ARV-110 and requires permanent discontinuation of ARV-110, abiraterone must also be permanently discontinued-.
- Any dosing interruption lasting >28 days with the following exceptions:
  - Dosing interruptions >28 days that occur for non-drug-related reasons may be allowed if approved by the Sponsor. Prior to re-initiating treatment in a patient with a dosing interruption lasting >28 days, the Sponsor must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted.
- Any AE, laboratory abnormality, or intercurrent illness that, in the judgment of the Investigator, presents a substantial clinical risk to the participant with continued ARV-110 treatment.

- If a clinically significant electrocardiogram (ECG) finding is identified (including, but not limited to changes from baseline in corrected QTcF after enrollment), the Investigator or qualified designee will determine if the patient can continue in the study and if any change in patient management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding will be reported as an AE. An exception may be granted in rare circumstances for which there is a compelling safety reason to allow the patient to continue. In these rare cases, the Investigator must obtain documented approval from the Sponsor or Sponsor designee to allow the patient to continue in the study.

8.4 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

The IP/IMP should be stored in a secure area according to local regulations. It is the responsibility of the Investigator to ensure that IP/IMP is only dispensed to study patients. The IP/IMP must be dispensed only from official study sites by authorized personnel according to local regulations.

The IP/IMP storage manager should ensure that the study treatment is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by Arvinas. If concerns regarding the quality or appearance of the study treatment arise, the study treatment should not be dispensed, and Arvinas should be immediately contacted.

IP/IMP documentation (whether supplied by Arvinas or not) must be maintained that includes all processes required to ensure study treatment is accurately administered. This includes documentation of IP/IMP storage, dispensing processes, and administration.

Further guidance and information for final disposition of unused study treatment are provided in the study Pharmacy Manual.

8.5 CLINICAL PRODUCT COMPLAINT

A clinical product complaint is defined as a problem or potential problem with the physical quality or characteristics of clinical drug supplies used in a clinical research study. Examples of a clinical product complaint include, but are not limited to, suspected contamination, questionable quality appearance, defective packaging components, missing or extra units, incorrect packaging or labelling, and unexpected taste or odor.

Any clinical product complaint associated with an IP supplied by the Sponsor is to be reported according to the instructions provided in the Pharmacy Manual. Each clinical investigator site will be responsible for reporting a possible clinical product complaint by completing the Product Complaint Form and emailing it to clinicalcomplaints@Arvinas.com within 2 business days of becoming aware.

8.6 TREATMENT COMPLIANCE

The prescribed dosage, timing, and mode of administration may not be changed, except as defined in Section 8.3. Any departures from the intended regimen must be recorded in the eCRFs.

ARV-110 will be administered orally QD with food (e.g., meal of ≥400 calories that includes a mixture of fat, carbohydrates, and protein) during each 28-day cycle (see Section 8.2). Abiraterone will be administered orally QD on an empty stomach during each 28-day cycle. Patients will self-dose, except for doses that will be administered at the clinic, as described in Table 3 and Table 4.

At each visit where additional study drug will be dispensed, the previously dispensed study treatment will be retrieved by the study center and compliance assessed. Patients will be required to return all bottles and remaining tablets of ARV-110 and abiraterone, as well as the completed patient diary for drug accountability and compliance. Patients are to complete the study drug diary daily during study participation; documentation of food consumption is required for C1 only. Patients exhibiting poor compliance as assessed by tablet counts should be counseled on the importance of good compliance to the study dosing regimen.

Treatment compliance will be monitored by drug accountability as well as the patient's medical record and eCRF.

8.6.1 Treatment Compliance for Patients on Treatment After Notice From Sponsor of Primary Study Completion

The prescribed dosage, timing, and mode of administration may not be changed, except as defined in Section 8.3. Any departures from the intended regimen must be recorded in the appropriate site source documentation system.

ARV-110 will be administered orally QD with food (e.g., meal of ≥400 calories that includes a mixture of fat, carbohydrates, and protein) during each 90-day cycle (see Table 5 and Section 8.2). Abiraterone will be administered orally QD on an empty stomach during each 90-day cycle.

At each visit where additional study drug will be dispensed, the previously dispensed study treatment will be retrieved by the study center and compliance assessed. Patients will be required to return all bottles and remaining tablets of ARV-110 and abiraterone. Patients should self-report any missed doses and reason. Patients exhibiting poor compliance as assessed by tablet counts should be counseled on the importance of good compliance to the study dosing regimen.

Treatment compliance will be monitored by drug accountability and documented in site source documents.

8.7 CONCOMITANT THERAPY

Any vaccine (see COVID-19 information in Appendix 9) or medication, including over-the-counter or prescription medicines, vitamins, physiologic replacement doses of systemically administered corticosteroids, and/or herbal supplements that the patient is receiving at the time of enrollment (within 28 days before the time of enrollment) or receives during the study must be recorded in the eCRF along with:

- Reason for use.
- Dates of administration including start and end dates.
- Dosage information including dose and frequency.

8.7.1 Permitted Therapy

Bisphosphonates and other receptor activator of nuclear factor kappa-B (RANK) ligand inhibitors are permitted on study.

Palliative radiation for the treatment of pain due to bone metastases and palliative surgery are permitted on study starting after C2D1 (after the DLT evaluation period). Full restaging scans should be completed within 4 weeks prior to initiation of palliative therapy. If patients have evidence of radiographic disease progression, patients may qualify for continuing treatment after discussion with the Medical Monitor if the Investigator determines they are still benefiting from study drug (e.g., improvement of cancer-related symptoms).

The Medical Monitor should be contacted if there are any questions regarding palliative therapy.

8.7.2 Prohibited and/or Restricted Treatments

Other therapies with known anti-cancer effects are prohibited during study participation.

Patients should not take stomach acid modifying agents (e.g., proton-pump inhibitors, H2 blockers, antacids) while taking ARV-110 as it may result in reduced ARV-110 exposure. If this is unavoidable, space these medications at least 10-12 hours before or after study drug administration.

Patients should **not** receive the following while participating in trials with ARV-110 and abiraterone (unless utilized with caution to treat a drug-related AE when no alternative is available):

- Sensitive BCRP substrates or substrates with narrow therapeutic indices
- Sensitive P-gp substrates or substrates with narrow therapeutic indices
- Sensitive CYP3A4 substrates or substrates with narrow therapeutic indices
- Strong CYP3A4 inhibitors and inducers
- Grapefruit, grapefruit juice, Seville oranges, Seville orange juice
- CYP2D6 substrates with a narrow therapeutic index (e.g., thioridazine)

See Appendix 2 for list of examples of these types of agents. Treatment with any of these agents should be discontinued at least 5 half-lives prior to starting ARV-110.

Any medications with known QT risk, and/or are that are associated with a risk of Torsades de Pointes, are prohibited within 7 days prior to first dose of ARV-110 and during the study, unless they are used with caution to treat a drug-related AE when no alternative is available (see Appendix 2). For additional information, including exceptions to excluded medications, refer to the IB and abiraterone local practice guidelines and package inserts.

Exceptions or substitutions must be discussed with and agreed to by the Arvinas' Medical Monitor in advance of patient enrollment or initiation of concomitant therapy in ongoing patients.

8.7.3 Other Restrictions and Precautions

As this is the first administration of the combination of ARV-110 and abiraterone to humans, all effects cannot be reliably predicted. Facilities and staff for resuscitation and the treatment of other medical emergencies should be available.

8.8 TREATMENT AFTER THE END OF THE STUDY

Following completion of the study, treatment for patients who have demonstrated a clinical benefit will be provided at the discretion of the Sponsor in accordance with local regulations, including approval by any responsible health authority and ethics committee, as appropriate.

For patients on treatment after notice from sponsor of primary study completion, see Table 5, Section 6.7, and Appendix 10.

9. STUDY STOPPING AND DISCONTINUATION CRITERIA

9.1 PATIENT DISCONTINUATION OF STUDY TREATMENT

Patients MUST discontinue all IP (and non-IP at the discretion of the Investigator) for any of the following reasons:

- Patient's request to stop study treatment. Patients who request to discontinue study treatment will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a patient specifically withdraws consent for any further contact with him/her or persons previously authorized by patient to provide this information.
- Any clinical AE, laboratory abnormality, or intercurrent illness that, in the opinion of the Investigator, indicates that continued participation in the study is not in the best interest of the patient.
- Termination of the study by Sponsor (Arvinas Androgen Receptor, Inc.).
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness.
- Criteria listed in Section 8.3.6.

- Disease recurrence or occurrence of a secondary malignancy that requires systemic therapy or radiotherapy for treatment.
- Evidence of radiographic disease progression with lack of clinical benefit.
- Death from any cause.

Refer to the SoA (Table 2) for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that can be completed.

All patients who discontinue study treatment should comply with protocol-specified follow-up procedures as outlined in the SoA (Table 2). The only exception to this requirement is when a patient withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study treatment is discontinued prior to the patient's completion of the study, the reason for the discontinuation must be documented in the patient's medical records and entered on the appropriate eCRF page.

9.2 CRITERIA FOR STOPPING THE STUDY

The Sponsor may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. The Investigator may also terminate the study at his/her site for reasonable cause, after providing written notice to the Sponsor in advance of the intended termination. Advance notice is not required by either party if the study is stopped due to safety concerns. If the Sponsor terminates the study for safety reasons, the Sponsor will immediately notify the Investigator by telephone and subsequently provide written instructions for study termination.

The Sponsor reserves the right to discontinue the study for medical and/or administrative reasons at any time.

Conditions that may cause termination of the study in its entirety or an individual study site may include but are not limited to:

- The discovery of an unexpected, serious, or unacceptable risk to any patient enrolled in the study.
- The Sponsor's decision to suspend or discontinue further testing or evaluation of the drug under study.
- The failure of the Investigator to comply with the approved protocol, appropriate guidelines, and applicable regulations.
- Submission of intentionally or knowingly false information from the Investigator to the Sponsor.

In the expansion phase, enrollment will be paused if the rate of discontinuations due to treatment related AEs exceeds 30% in a population consisting of a minimum of 15 patients, until the SRC has reviewed the data and confirmed the event rate.

9.3 PATIENT WITHDRAWAL FROM THE STUDY

Patients who request to discontinue study treatment will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a patient specifically withdraws consent for any further contact with him/her or persons previously authorized by patient to provide this information.

- Patients should notify the Investigator of the decision to withdraw consent from future follow-up in writing, whenever possible.
- The withdrawal of consent should be explained in detail in the medical records by the Investigator, as to whether the withdrawal is from further treatment with study treatment only or also from study procedures and/or post-treatment study follow-up, and entered on the appropriate eCRF page.
- In the event that vital status (whether the patient is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.
- If the patient withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

9.4 LOST TO FOLLOW-UP

- All reasonable efforts must be made to locate patients to determine and report their ongoing status. This includes follow-up with persons authorized by the patient.
- Lost to follow-up is defined by the inability to reach the patient after a minimum of **3** documented phone calls, faxes, or emails as well as lack of response by patient to 1 registered mail letter. All attempts should be documented in the patient's medical records.
- If it is determined that the patient has died, the site will use permissible local methods to obtain date and cause of death.
- If Investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the patient's informed consent, then the Investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining patient's contact information or other public vital status data necessary to complete the follow-up portion of the study.
- The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information.
- If after all attempts, the patient remains lost to follow-up, then the last known alive date as determined by the Investigator should be reported and documented in the patient's medical records.

10. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Section 3).

- Protocol waivers or exemptions are not allowed without Sponsor approval.
- All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in the SoA (Table 3), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria before enrollment. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the patient's prior clinical management (e.g., blood count, CT scans, viral testing) and obtained before signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the SoA.

Additional measures, including non-study required laboratory tests, should be performed as clinically indicated or to comply with local regulations. Laboratory toxicities (e.g., suspected drug-induced liver enzyme evaluations) will be monitored during the follow-up phase via on-site/local labs until all study drug-related toxicities resolve, return to baseline, or are deemed irreversible.

Some of the assessments referred to in this section may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

The blood volume collected from each patient is detailed in the Laboratory Manual. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

10.1 SAFETY

Safety will be evaluated through AE monitoring, clinical evaluations (i.e., vital signs, PE, ECGs), and laboratory tests (i.e., hematology, serum chemistries).

Any clinically significant changes, in the opinion of the Investigator, noted during abbreviated or final physical examinations, ECG evaluations, and any other safety assessments, whether or not these procedures are required by the protocol, should also be recorded in the appropriate AE page of the eCRF, including information regarding NCI CTCAE version 5.0 grade, relationship to study drug, any action taken, date of onset, and outcome (Section 10.2).

Planned time points for all safety assessments are listed in the SoA (Section 3).

10.1.1 Physical Examinations

A complete physical examination (PE) will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, musculoskeletal, and neurological systems. An abbreviated PE will be symptom directed.

The PE should be performed by the same person each time when possible. Investigators should pay special attention to clinical signs related to previous serious illnesses.

10.1.2 Vital Signs

Temperature assessments may be oral or tympanic. Blood pressure (BP) and pulse measurements will be assessed while the patient is in a sitting position or semi-recumbent position (recommended). The same position should be used throughout the study. Manual techniques will be used only if an automated device is not available.

BP and pulse measurements should be preceded by approximately 5 minutes of rest for the patient in a quiet setting without distractions (e.g., television, cell phones).

10.1.3 Electrocardiograms

12-lead ECG(s) will be obtained using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. See also Section 11.3.1.4. All 12-lead ECGs should be confirmed by qualified personnel at the institution and may be reviewed by a central laboratory.

Refer to Section 8.3.6 for QTc withdrawal criteria.

10.1.4 Clinical Safety Laboratory Assessments

See Appendix 4 for the list of clinical laboratory tests to be performed and the SoA (Section 3) for the timing and frequency.

The Investigator must review the laboratory report, document their review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease/patient's health status, unless judged by the Investigator to be more severe than expected for the patient's condition.

All laboratory tests with values considered abnormal and clinically significant during participation in the study or within 35 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.

For patient convenience, the blood tests performed during any non-clinic visit day may be performed at the study center or locally (i.e., licensed laboratory) and the lab results sent to the Principal Investigator.

All protocol-required laboratory assessments, as defined in Appendix 4, must be conducted in accordance with the Laboratory Manual and the SoA (Section 3). Appendix 4 and the SoA also includes information on allowable windows for testing and windows for screening tests to be used for C1D1.

If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in patient management or are considered clinically significant by the Investigator (e.g., serious adverse event [SAE], AE, or dose modification), then the results must be recorded in the eCRF.

10.1.5 Imaging Safety Assessment

Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the Study Investigator as per standard medical/clinical judgment.

10.2 ADVERSE EVENTS

Note: After notice from Sponsor of primary study completion, clinical data will no longer be recorded in the eCRF. Clinical data will be recorded only in the site source. For patients on treatment after primary study completion, modified collection and reporting of AEs is described in Section 10.2.1.1 and Appendix 5.

The definitions of an AE or SAE are in Appendix 5. AEs should be documented and recorded at each visit and graded using the NCI CTCAE version 5.0.

AEs will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative).

The Investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the patient to discontinue before completing the study (see Section 9).

10.2.1 Time Period and Frequency for Collecting AE and SAE Information

The collection of non-serious AE information should begin at initiation of study treatment until 30 days after the last dose at the timepoints specified in the SoA (Section 3).

The ARV-110 IB provides the Reference Safety Information to determine expectedness of SAEs for expedited reporting of ARV-110. (See also the current abiraterone prescribing information, as applicable.) Following the patient's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures.

All SAEs must be collected that occur during the screening period through 30 days of discontinuation of dosing. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (e.g., a follow-up skin biopsy). For patients enrolled and never treated with study drug, SAEs should be collected for 30 days from the date of enrollment.

The Investigator must report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure.

Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the appropriate section of the eCRF.

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours of becoming aware of the event, as indicated in Appendix 5.

The Investigator will submit any updated SAE data to the Sponsor within 24 hours of this being available.

Investigators are not obligated to actively seek AEs or SAEs in former study patients. However, if the Investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the Investigator must promptly notify the Sponsor.

The method of evaluating and assessing causality of AEs and SAEs and the procedures for completing and reporting/transmitting SAE reports are provided in Appendix 5.

10.2.1.1 Alternate Collection and Reporting of SAEs, Deaths Due to Disease Progression and AEs Leading to Discontinuation of Study Drug After Notice From Sponsor of Primary Study Completion

The following events must be reported to the sponsor:

- SAEs
- Deaths due to disease progression
- AEs leading to discontinuation of study drug.
    - This includes clinically significant changes, in the opinion of the investigator, noted during standard of care safety assessments (physical exam, vital signs, ECOG, laboratory values, ECG evaluations, etc.) leading to discontinuation.

All reporting to sponsor should follow the Reporting of SAEs, Deaths Due to Disease Progression, and AEs Leading to Discontinuation of Study Drug After Notice From Sponsor of Primary Study Completion in Appendix 5.

Note: Non-serious AEs, excluding the events listed above, will not be reported to the Sponsor, but will be recorded in site source.

10.2.2 Method of Detecting AEs and SAEs

AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a patient. In order to prevent reporting bias, patients should not be questioned regarding the specific occurrence of 1 or more AEs.

10.2.3 Follow-up of AEs and SAEs

Treatment-related non-serious AEs should be followed to resolution or stabilization or reported as SAEs if they become serious (see Appendix 5).

Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study treatment and for those present at the end of study treatment as appropriate.

All identified non-serious AEs must be recorded and described on the non-serious AE page of the case report form (CRF; paper or electronic). Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

After the initial AE/SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the patient is lost to follow-up (as defined in Section 9.2).

Further information on follow-up procedures is given in Appendix 5.

10.2.4 Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator to the Sponsor of SAEs is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a product under clinical investigation are met.

An Investigator who receives an Investigator safety report describing SAEs or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

The Sponsor or designee will report AEs to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC and FDA 21 *Code of` Federal Regulations* (CFR) Parts 312 and 320. A SUSAR (Suspected, Unexpected Serious Adverse Reaction) is a subset of SAEs and will be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

10.2.5 Pregnancy

If a male patient's female partner is found to be pregnant while the patient is being treated or within 16 weeks of their last dose, the Investigator must submit the "pregnancy reporting and outcome form" through the SAE reporting process. The patient may continue in the study if an accidental pregnancy in the female partner occurs despite adequate contraception. Details of all

pregnancies in female partners of male patients will be collected after the start of study treatment and until 16 weeks after the last dose of study drug.

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 5.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs. Pregnancy or elective abortion itself is not considered an AE unless there is a suspicion that IP may have interfered with the effectiveness of the contraceptive medication.

10.2.6 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the non-serious AE CRF page or SAE Report Form as appropriate (paper forms are only intended as a back-up option when the electronic system is not functioning):

- Any laboratory test result that is clinically significant or meets the definition of an SAE.
- Any laboratory test result abnormality that required the patient to have study treatment discontinued or interrupted.
- Any laboratory test result abnormality that required the patient to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting Investigator (e.g., anemia versus low hemoglobin value).

10.2.7 Potential Drug-Induced Liver Injury

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential drug-induced liver injury (DILI) event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs.

Potential DILI is defined as:

- Aminotransferase (AT; ALT or AST) elevation >3× ULN,

AND

- Total bilirubin >2× ULN, without initial findings of cholestasis (elevated serum ALP),

AND

- No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

10.2.8 Other Safety Considerations

Any significant worsening noted during interim or final PEs, ECG, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a non-serious or serious AE, as appropriate, and reported accordingly.

10.3 OVERDOSE

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 10.2).

10.4 EFFICACY ASSESSMENTS

Tumor assessment(s) for the patient should continue as per protocol even if dosing is interrupted and will take place in accordance with the SoA in Section 3.

10.4.1 Imaging and Clinical Assessment

To meet the study's secondary objectives related to assessment of anti-tumor response, preliminary antitumor activity of ARV-110 in combination with abiraterone will be evaluated through assessment of PSA levels, imaging, tumor assessment, and assessment of bone and soft tissues. Planned time points for all efficacy assessments are provided in the SoA.

Procedures conducted as part of the patient's routine clinical management (e.g., computed tomography [CT], bone scan) and obtained before signing of the ICF may be utilized for screening or baseline purposes, provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

10.4.2 Radiographic Imaging

Radiographic imaging, including bone scans and CT or magnetic resonance imaging (MRI) for all known or suspected disease sites, is required during Screening. Brain scans (if suspected central nervous system [CNS] metastases present) and bone scans will be performed at Baseline and on study according to the SoA (Section 3).

Tumor assessments will include all known or suspected disease sites. Imaging will include chest, abdomen, and pelvis CT or MRI scans (same modality should be used throughout the study). If MRI is performed for the abdomen and pelvis examinations at Baseline, then at least a non-contrast CT of the chest must be performed as well. CT or MRI scans to be done every 8 weeks (i.e., Days 56, 112, and 168 [± 5 days]) from C1D1 then every 12 weeks (±5 days) thereafter. Time points are fixed and calculated from C1D1 based on the calendar, regardless of treatment interruptions. Tumor assessments are to continue until radiographically and/or clinically (i.e., for photographed or palpable lesions) documented disease progression as per modified RECIST 1.1/PCWG3, discontinuation of study treatment, initiation of subsequent systemic anti-cancer therapy, or withdrawal of consent (whichever occurs first). Given the exploratory nature of the study, confirmation of response (complete response [CR] or partial response [PR]) is recommended per Appendix 7.

All patients who discontinue study treatment for reasons other than disease progression (e.g., AE) should continue to have tumor assessments as per the schedule and until disease progression or until subsequent anti-cancer therapy is initiated.

10.4.3 Tumor Assessment

Soft tissue disease response and progression will be defined per modified PCWG3 and RECIST 1.1 guidelines (Appendix 7). Analysis of tumor assessments for this study will be by Investigator assessment and will be collected on eCRF.

Soft Tissue Disease Assessment

The CT scans should include full coverage of chest, abdomen, pelvis, and any additional area of interest at all specified time points (at Screening, every 8 weeks (i.e., Days 56, 112, and 168 [±5 days]) from C1D8, and then every 12 weeks (±5 days) thereafter). If MRI is performed for the abdomen and pelvis examinations, then at least a non-contrast CT chest scan must be performed as well. Baseline CNS imaging is not required with the exception of symptomatic patients to rule out CNS metastases. The same method of radiographic assessment should be used throughout the study.

10.4.4 Bone Scan Assessment

Whole-body anterior and posterior bone scans should be acquired using technetium 99m-methyl diphosphonate (Tc99 MDP) administered intravenously (IV), with imaging performed approximately 3 hours (2-4 hours) after injection. For post baseline bone scans, the same imaging protocol (i.e., dose, circulation time, bed speed) should be followed for all follow-up imaging visits.

For patients with symptoms of spinal compression, MRI of the spine and base of the skull should also be performed.

Bone scans are to be done at Screening and then every 8 weeks (i.e., Days 56, 112, and 168 [±5 days]) from C1D1, and then every 12 weeks (±5 days) thereafter. Changes in lesions that are considered metastatic on bone scintigraphy should be followed and assessed serially using a bone scan assessment form (see Appendix 7). Worsening bone scan does not warrant discontinuation of bone scans or study treatment.

10.4.5 Imaging Restrictions and Precautions

Table 11 provides a summary of the alternative methods, acceptable per protocol, in the event of contraindications for use of IV and oral contrast, and or/MRI.

Table 11. Acceptable Imaging Assessment Methods for Different Anatomic Regions

Anatomic Region	Preferred Method	Alternative Methods	Notes
Chest, abdomen, and pelvis Note: Scan must cover lung apices to diaphragm, diaphragm through entire liver, and to below the pubic symphysis.	CT with IV contrast	**For chest:** • CT without contrast can be used only if the patient has a clinical contraindication for iodine-based IV contrast (e.g., hypersensitivity, renal insufficiency) **For abdomen and pelvis:** • MRI with gadolinium-based IV contrast is the first alternative method if the patient has a clinical contraindication for iodine-based IV contrast • CT without contrast can be used as the second alternative method only if the patient has a clinical contraindication for both contrast-enhanced CT and MRI	• CT scans must be performed with slice thickness of ≤5 mm. The reconstruction interval should be equal to slice thickness to avoid gap. • For abdomen and pelvis CT scans, oral contrast is recommended as per institutional standards.
Brain	MRI with IV contrast	CT with IV contrast is the first alternative method if IV gadolinium is clinically contraindicated. MRI without contrast can be used as a second alternative method if a patient has clinical contraindications for both contrast-enhanced CT and MRI	• MRI should include both T1 and T2-weighted sequences with T1-weighted both and pre- and post-contrast.
Bone	Bone scintigraphy	99mTc-hydro-xymethane diphosphonate (99mTc-HDP), PET (^{18}F-fluoride NaF) and 99m Technetium SPECT	• If bone scan shows hotspots indicative of metastases, further investigation with x-ray, CT, or MRI is warranted.

Abbreviations: CT=computed tomography; IV=intravenous(ly); MRI=magnetic resonance imaging; PET = positron emission tomography; SPECT=single photon emission computed tomography.

Note: The same modality for a given anatomical coverage and the same scanning procedure (most importantly: reconstruction slice thickness, anatomic coverage, use of IV contrast) should be consistent between baseline and all subsequent follow-up scanning. If possible, the same scanner or an equivalent scanner should be used throughout the study.

If gadolinium is contraindicated, proceed without contrast, but the reason for not using contrast must be documented.

10.5 PHARMACOKINETICS

10.5.1 Collection of Blood Samples for PK Analysis

Blood sampling for PK analysis will be conducted as specified in the SoA (Section 3). All time points are relative to the start of abiraterone administration. On days of scheduled clinic visits for extensive PK blood collections, patients should be instructed to not take abiraterone and ARV-110 at home, and that it will be given in the clinic.

10.5.2 Collection of Samples

Venous blood samples will be collected for the determination of abiraterone and ARV-110 PK (Table 3 for intensive PK sampling and Table 4 for sparse PK sampling).

The blood volume of PK samples required for each study drug is specified in the Laboratory Manual. Additional samples may be collected at additional time points during the study if agreed upon between the Investigator and the Sponsor for further assessment of an observed toxicity.

For visits with PK sampling, the actual date and time (24-hour clock time) of any dose of abiraterone (if applicable) or ARV-110 given in clinic, and the actual date and time of each blood sample for PK will be collected and recorded in the eCRF. The dates/times of the last oral IP dose prior to a PK sampling visit, as reported by the patient, will also be recorded. PK samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

10.5.3 Determination of Drug Concentration

PK samples for the determination of abiraterone, and total ARV-110 in plasma will be analyzed using either a validated stereospecific or non-stereospecific bioanalytical method, as appropriate. Full details of the stereospecific and non-stereospecific bioanalytical methods will be described in separate bioanalytical reports. All PK samples within the known stability window at the time of receipt by the bioanalytical laboratory will be analyzed. Plasma samples may be subjected to further analysis by the Sponsor or designee for the purpose of the development of additional bioanalytical assays and/or to investigate the presence biotransformation products of total ARV-110 and its enantiomers, ARCC-51A and ARCC-51B.

10.5.4 Calculation of Pharmacokinetic Variables

Pharmacokinetic parameters of abiraterone, and total ARV-110, will be derived using noncompartmental methods with Phoenix® WinNonlin® version 8.0 or higher (Certara, L.P. Princeton, New Jersey, US) and/or SAS® version 9.2 or higher (SAS Institute, Inc., Cary, North Carolina, US) if data allow. Actual elapsed time from dosing will be used for the final plasma PK parameter calculations.

10.5.5 Plasma Pharmacokinetic Parameters

The following PK parameters of abiraterone, and total ARV-110 will be assessed using noncompartmental methods, if data allow (Table 12). Other PK parameters of abiraterone, and total ARV-110 may also be calculated as appropriate.

Table 12. Pharmacokinetic Parameters of Abiraterone, and Total ARV-110 Following Single and Multiple Dosing

Pharmacokinetic Parameter	Definition
C_{max}	Maximum observed concentration, occurring at time T_{max}
T_{max}	Time of maximum observed concentration
C_{min}	Minimum plasma concentration, obtained directly from the observed concentration versus time data
AUC_{last}	Area under the plasma concentration-time curve from the time of dosing to the time of the last measurable (positive) concentration (T_{last})
AUC_{tau}	Area under the plasma concentration-time curve from time zero during a dosing interval, calculated by linear up/log down trapezoidal summation
T_{last}	Time of last measurable (positive) observed concentration
C_{last}	Observed concentration corresponding to T_{last}

10.6 [redacted]

[redacted]

10.7 COVID-RELATED GUIDANCE

COVID-related guidance, including information about receiving vaccine before or during the study, use of TeleMed visits, and how to handle positive COVID-19 test results, is provided in Appendix 9.

11. STATISTICAL CONSIDERATIONS

The primary objectives of this study are to evaluate the safety and tolerability of ARV-110 in combination with abiraterone, and to determine the RP2D administered orally among male patients with mPC who have rising PSA, without radiographic progression of their disease, while receiving abiraterone and concomitant corticosteroid therapy.

The RP2D will be based on safety and available PK data. AEs and SAEs will be tabulated by system organ class and preferred terms. Laboratory test results after the first dose of ARV-110 in combination with abiraterone will be summarized with regard to shifts from baseline values. All AEs will be graded according to NCI CTCAE version 5.0.

Details of the statistical analyses presented below and additional analyses of all clinical, safety, PK, and laboratory data will be provided in the study's Statistical Analysis Plan (SAP).

If data allow, descriptive statistics will be used to display the data and results. Continuous variables, including baseline characteristics, will be summarized by reporting the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical/discrete variables will be summarized using frequency tables showing the number and percentage of patients within a category. Efficacy data will be presented in listings and with swim lane plots.

11.1 SAMPLE SIZE DETERMINATION

Approximately 40 patients will be treated to evaluate the safety profile and preliminary antitumor activity of ARV-110 in combination with abiraterone. Assuming the target PSA control rate (as measured by lack of PSA progression at 12 weeks) ranges from 30% to 90%, given total sample size 40, the width of corresponding 95% CIs per the Clopper-Pearson exact method will be 0.21 to 0.33. A detailed table is provided in Table 13. Patients whose baseline scans show radiographic progression (compared to the last scans obtained prior to study enrollment) may be replaced to ensure a minimum of 40 study patients with PSA-only progression on abiraterone at study entry.

Table 13. 95% Confidence Intervals of PSA Control Rate

Total Sample Size	Number of Subjects with PSA Control	PSA Control Rate	95% CI lower limit	95% CI upper limit
40	12	0.30	0.17	0.47
40	14	0.35	0.21	0.52
40	16	0.40	0.25	0.57
40	18	0.45	0.29	0.62
40	20	0.50	0.34	0.66
40	22	0.55	0.38	0.71
40	24	0.60	0.43	0.75
40	28	0.70	0.53	0.83
40	32	0.80	0.64	0.91
40	36	0.90	0.76	0.97

Abbreviations: CI=confidence interval; PSA= prostate-specific antigen.

11.2 POPULATIONS FOR ANALYSES

11.2.1 Enrolled Analysis Set

The Enrolled analysis set consists of patients who are registered to participate in this study with informed consent signed and have successfully undergone the inclusion/exclusion criteria assessment.

11.2.2 Safety Analysis Set

The Safety analysis set consists of enrolled patients receiving any amount of study drug (ARV-110 dose or abiraterone). The Safety analysis set will be used for the summary of demographic and baseline characteristics, medical history, and pre-existing conditions of patients, AEs, and laboratory results. In addition, rPFS analysis will be based on the Safety analysis set.

11.2.3 Dose-Limiting Toxicity Analysis Set

The DLT analysis set includes all patients from safety lead-in who receive at least 80% of their planned dose of ARV-110 in combination with abiraterone in the first 4 weeks of the combination treatment, and all patients who receive less than 80% of their planned dose of ARV-110 in combination with abiraterone in the first 4 weeks due to a treatment-related DLT.

11.2.4 Pharmacokinetic Data Analysis Set

The PK data analysis set will include all patients who have received at least 1 dose of ARV-110 and abiraterone and have provided at least 1 blood sample for PK analysis with measurable concentration. The patients in the PK data analysis set should have adequate study medication compliance, without any relevant protocol violations, events, or concomitant medications likely to affect the PK of abiraterone and total ARV-110.

11.2.5 Prostate-Specific Antigen Efficacy Analysis Set

The PSA Efficacy analysis set will be composed of all ARV-110 and abiraterone treated patients with baseline PSA assessment and at least a C2D1 or later PSA assessment (i.e., at least 4-weeks post-baseline). The PSA Efficacy analysis set will be used for the summary of the PSA-related efficacy endpoints and follow recommendations per PCWG3.

11.2.6 Response Efficacy Analysis Set

The Efficacy analysis set will be comprised of all patients treated with both ARV-110 and abiraterone in the Safety analysis set with baseline and at least 1 post-baseline radiographic assessment (CT/MRI scan) for RECIST 1.1 related efficacy endpoints. Overall response rate (ORR) per modified RECIST 1.1/PCWG3 will be based on Response Efficacy analysis set for subjects with measurable disease at baseline.

11.2.7 [redacted]

11.3 STATISTICAL ANALYSES

This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

11.3.1 Safety Analyses

11.3.1.1 Adverse Event and Serious Adverse Events

All AEs recorded in the eCRFs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) (version 20.1 or higher) and graded using NCI CTCAE version 5.0. TEAEs will be summarized by system organ class, preferred term, and/or maximum CTCAE grade in each treatment cohort, including number and percentage of patients with TEAEs, serious TEAEs, TEAEs that lead to discontinuation, and TEAEs that lead to death.

Causality of TEAEs being considered as “Probably related” or “Possibly related” by Principal Investigators will be defined as treatment related. Any TEAEs with missing causality will be classified conservatively as treatment-related. The treatment-related TEAEs and serious TEAEs will be summarized.

The number and percentage of patients with DLTs will be reported for DLT population. The details of DLT will be listed.

11.3.1.2 Laboratory Tests

The absolute values and change from baseline of each parameter in hematology, blood chemistry, and coagulation test will be summarized with n, mean, standard deviation, median, minimum, and maximum values by visit. The shift of the post-baseline toxicity grade from baseline will be tabulated by visit. The shift of the worst post-baseline toxicity grade from baseline will be summarized as well. The absolute values and change from baseline of gravity and pH in urinalysis will be summarized with n, mean, standard deviation, median, minimum,

and maximum values by visit. The shift of the other urinalysis parameter normality/abnormality from baseline will be tabulated by visit.

The number and percentage of patients with elevated AST, ALT, total bilirubin (Tbil), and ALP will be summarized for the Safety Analysis Set. Elevations will be summarized as a function of the ULN.

- 3× ULN, 5× ULN, 10× ULN, and 20× ULN elevations of AST, ALT, and either ALT or AST.
- Any elevations of bilirubin; elevated total bilirubin to >2× ULN.
- Any elevations of ALP >1.5× ULN.
- Elevation of ALT/AST (>3× ULN) accompanied by elevated bilirubin (>1.5× ULN, >2× ULN).

11.3.1.3 Vital Signs

Vitals signs (e.g., weight, heart rate, respiratory rate [RR], systolic BP, diastolic BP, and body temperature) will be summarized by visit.

- Change from baseline by visit (including mean, median, standard deviation, maximum, and minimum).
- Percentage change from baseline at each visit through treatment discontinuation.

11.3.1.4 Electrocardiogram

The QTcF interval, QT interval correction by Bazett's method (QTcB), and other ECG parameters will be summarized numerically and categorically using the Safety analysis set.

- Change of ECG parameters from baseline by visit (including mean, median, standard deviation, maximum, and minimum).
- The number and percentage of patients with maximum on treatment QTcF/QTcB values <450, ≥450 to <480, ≥480 to <500, ≥500 msec.
- The number and percentage of patients with the QTcF/QTcB changes as <30, ≥30 to <60, ≥60 msec.

QTcF interval and QTcB interval will be calculated with the following formulas:

- $QTcB = QTc/(RR^{1/2})$
- $QTcF = QTc/(RR^{1/3})$

If duplicate/triplicates of QTcB/QTcF are available at 1 time point, the average of each parameter will be derived for the summary.

11.3.1.5 Physical Examinations

All PE results will be listed.

11.3.2 Efficacy Analyses

The RECIST 1.1 and PCWG3 criteria are available in Appendix 7. Efficacy results will be summarized in listings.

For the binary endpoints such as PSA control rate, PSA response rate, and ORR, analysis will be based on all corresponding response evaluable subjects. The estimate of PSA control rate/PSA response rate/ORR and the corresponding 2-sided 95% CI will be calculated using the Clopper-Pearson exact method.

11.3.2.1 PSA Control Rate and Prostate-Specific Antigen Response Rate

The PSA control is defined as the status of lack of PSA progression on study. The PSA progression is defined as a ≥25% increase in PSA and an absolute increase of PSA ≥2 ng/mL above the nadir, which is confirmed by a second consecutive value obtained 3 or more weeks later.

A PSA_{50} response is defined as a ≥50% decline in PSA from Cycle 1 Day 1 (baseline) PSA value. This PSA decline must be confirmed to be sustained by a second PSA value obtained 3 or more weeks later. The PSA_{50} response rate is the proportion of patients with a PSA_{50} response The PSA_{30} response rate is defined similarly with a cutoff of 30% instead of 50%.

The estimate of PSA control rate/PSA response rate and the corresponding 2-sided 95% CI will be calculated using the Clopper-Pearson exact method.

In addition, the effects of ARV-110 and abiraterone on PSA will also be measured as absolute value, absolute change, and percent change from baseline (rise or fall) at each cycle Day 1. The best percent change of PSA from baseline, defined as the maximum decrease/or minimum increase of each patient, will be presented in a waterfall plot.

11.3.2.2 Best Overall Response and ORR

The PCWG3 advised CT or MRI scans will be done every 8 weeks (±5 days) for the first 6 months of study treatment, then every 12 weeks (±5 days) until the third year of study treatment, and every 6 months (±5 days) thereafter. The RECIST 1.1 (soft tissue) will be used to determine each patient's visit response according to target lesion, non-target lesion, and new lesion per the investigator. The overall response categories by visit include: CR, PR, stable disease (SD), indeterminate, and progressive disease. The treated patient who has baseline tumor assessment without post-baseline tumor assessment will be defined as not evaluable. The patient best overall response will be determined according to all visit response by the following sequential: CR, PR, SD, indeterminate, and progressive disease. The best overall response will be summarized in a listing by dose cohort.

The best percent change of the sum of target lesions from baseline, defined as the maximum decrease/or minimum increase of each patient, will be presented in a waterfall plot.

ORR is defined as the proportion of subjects whose best objective response (BOR) is a confirmed CR or confirmed PR, as determined by the Investigator. Analysis of ORR will be based on response efficacy analysis set for subjects with measurable disease at baseline. The estimate of ORR and the corresponding 2-sided 95% CI will be calculated using the Clopper-Pearson exact method.

11.3.2.3 Time to Event

For the time to event endpoints of time to PSA progression, duration of response (DOR), and rPFS, estimation will be done using Kaplan-Meier (KM) product-limit method. For radiographic DOR, analysis will be performed for subjects who achieve PR or CR. Analysis of rPFS will be based on all treated subjects. Median values along with two-sided 95% CI will be calculated. Summary statistics will be computed constructed based on a log-log transformed CI for the survivor function S(t).

Time to PSA Progression

Time to PSA progression is the time interval from the date of first ARV-110 dose to the date of PSA progression. The PSA progression date is defined as the date that a ≥25% increase and an absolute increase of ≥2 ng/mL above the nadir is documented, which is confirmed by a second consecutive value obtained 3 or more weeks later. The participants who do not have PSA progressing will be censored on the date of the last PSA assessment before receipt of new anticancer therapy. If the participant does not have post-baseline PSA assessment, the participant will be censored on the date of first ARV-110 dose.

Duration of PSA_{30} and PSA_{50} Response (decline of ≥30% and ≥50%, respectively)

Duration of PSA_{30} or PSA_{50} response is the time interval from the date of first PSA_{30} or PSA_{50} PR to the date of PSA progression. The PSA progression date is defined as the date that a ≥25% increase and an absolute increase of ≥2 ng/mL above the nadir is documented, which is confirmed by a second consecutive value obtained 3 or more weeks later. The patients who do not have PSA progressing will be censored on the date of the last PSA assessment before receipt of new anti-cancer therapy.

Radiographic Progression-free Survival

PFS is the time interval from the date of first ARV-110 dose to the date of first progression per modified RECIST 1.1/PCWG3, or death due to any cause, whichever occurs first. The patients who are alive or do not progress will be censored on the date of the last disease assessment before receipt of new anticancer therapy. If the patient is alive and does not have post-baseline imaging assessment, the patient will be censored on the date of first study drug dose.

Duration of Radiographic Response

DOR is defined as the time between the date of response to the date of the first documented tumor progression (per modified RECIST 1.1/PCWG3), as determined by the Investigator, or death due to any cause, whichever occurs first.

11.3.3 Pharmacokinetic Analyses

Plasma samples will be analyzed to explore effects of covariates such as age on PK, exposure-safety, and exposure-efficacy relationships.

If data allow, noncompartmental and/or compartmental methods will be used to calculate PK parameters, from plasma concentration-time data. Descriptive statistics (including number, mean and/or median, standard deviation, coefficient of variation, and range) for PK parameters will be tabulated by cohort, dose level, analyte, cycle, and day.

If data allow, PK data from this study may be combined with data from other studies and analyzed using population PK approach. Concentration-QTc analysis may be conducted using the PK and ECG data from this study or may be combined with other studies and reported separately. In addition, exposure-response relationship may be explored with PK and pharmacodynamics data from this study or combined with data from other studies; results of PK/pharmacodynamics analysis will also be reported separately.

Additional details of the statistical analyses for PK will be provided in the SAP.

11.3.4 [redacted] and Other Analyses

[redacted]

11.3.4.1 Subgroup Analyses

Prespecified subset analyses will be detailed in the SAP.

12. SAFETY REVIEW COMMITTEE

An SRC will be established to review the safety and PK data from patients enrolled into the study. The SRC will be comprised of Sponsor personnel responsible for the execution and safety oversight of this clinical trial as well as selected Principal Investigators. The SRC will be responsible for monitoring the ongoing safety data of patients enrolled in the study on a quarterly basis (or on an ad hoc basis as necessary), beginning with the enrollment of the first patient and continuing up to notice from Sponsor of primary study completion. Thereafter, the SRC will meet on an ad hoc basis for review of any new clinically significant safety events.

Additional details will be provided in the SRC Charter.

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14. APPENDICES

Appendix 1. Abbreviations

Abbreviation	Definition
ADT	androgen deprivation therapy
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APTT	activated partial thromboplastin time
AR	androgen receptor
AR-V	AR variant
AST	aspartate aminotransferase
AT	aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{0-24}	area under the plasma concentration-time curve from time zero to 24 hours
AUC_{last}	area under the plasma concentration-time curve from time zero to the time of last quantifiable concentration, calculated by linear up/log down trapezoidal summation
AUC_{tau}	area under the plasma concentration-time curve from time zero during a dosing interval, calculated by linear up/log down trapezoidal summation
BCRP	breast cancer resistance protein
BID	twice daily
BOIN	Bayesian Optimal Interval Design
BOR	best objective response
BP	blood pressure
BUN	blood urea nitrogen
CBC	complete blood count
CFR	*Code of Federal Regulations*
CI	confidence interval
C_{last}	observed concentration corresponding to T_{last}
C_{max}	maximum plasma concentration, obtained directly from the observed concentration versus time data
C_{min}	minimum plasma concentration, obtained directly from the observed concentration versus time data
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COVID	coronavirus disease 19
CR	complete response
CRF	case report form
CRPC	castration (castrate)-resistant prostate cancer
CSPC	castration (castrate)-sensitive prostate cancer
CT	computed tomography
[redacted]	[redacted]
CTCAE	Common Toxicity Criteria for Adverse Events

Abbreviation	Definition
[redacted]	[redacted]
CTFG	Clinical Trials Facilitation and Coordination
DDI	drug-drug interaction(s)
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOT	end of treatment
FDA	Food and Drug Administration
FIH	first in human
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GnRH	gonadotropin-releasing hormone
Hgb	hemoglobin
HIV	human immunodeficiency virus
HR	hazard ratio
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council of Harmonisation
IEC	Independent Ethics Committee
INR	international normalized ratio
IP/IMP	investigational product/investigational medicinal product
IRB	Institutional Review Board
IRT	interactive response technology
ID	identifier
IV	intravenous(ly)
KM	Kaplan-Meier
LDH	lactate dehydrogenase
LFT	liver function test
MB	myocardial band
mCRPC	metastatic castration-resistant prostate cancer
mCSPC	metastatic castration-sensitive prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
mOS	median overall survival
mPC	metastatic prostate cancer
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NSG	NOD scid- IL2Rγ
ORR	overall response rate
OS	overall survival
PCWG3	Prostate Cancer Working Group 3

Abbreviation	Definition
PD	progressive disease
PDX	patient-derived xenograft
PE	physical examination
PFS	progression-free survival
P-gp	P-glycoprotein
pH	potential of hydrogen
PK	pharmacokinetic(s)
PO	per oral/orally
PR	partial response
PROTAC®	PROteolysis Targeting Chimera
PSA	prostate-specific antigen
$PSA_{30,50}$	a ≥30% or ≥50% decline in PSA from Cycle 1 Day 1 (baseline) PSA value
PT, PTT	prothrombin time, partial thromboplastin time
QD	once daily
Q3W	every 3 weeks
QTcB	corrected QT interval by Bazett's method
QTcF	corrected QT interval by Fridericia's method
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
rPFS	radiographic progression-free survival
RR	respiratory rate
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SoA	Schedule of Activities
SRC	Safety Review Committee
Tbil	total bilirubin
99mTc-HDP	99mTc-hydro-xymethane diphosphonate
Tc99 MDP	technetium 99m-methyl diphosphonate
TEAE	treatment-emergent adverse event
TGI	tumor growth inhibition
T_{last}	time of last measurable (positive) observed concentration
T_{max}	time of maximum observed concentration (C_{max})
TRAE	treatment-related adverse event
ULN	upper limit of normal
US	United States
USPI	United States Package Insert
VCaP	vertebral cancer of the prostate
WOCBP	woman/women of childbearing potential

Appendix 2. Examples of BCRP, P-gp, and CYP3A4 Substrates; CYP2D6 Substrate with Narrow Therapeutic Index; and CYP3A4 Inhibitors and Inducers

Patients should **not** receive any of the following substrates if considered sensitive or having a narrow therapeutic index while participating in trials with ARV-110 (unless utilized with caution to treat a drug-related AE when no alternative is available): BCRP substrates, P-gp substrates, CYP3A4 substrates.

Patients should not receive strong CYP3A4 inhibitors and inducers, grapefruit, grapefruit juice, Seville oranges and Seville orange juice while participating in trials with ARV-110 (unless utilized with caution to treat a drug-related AE when no alternative is available).

Note: These lists are examples and are not intended to be exhaustive.

- Examples of BCRP substrate and P-gp substrate considered sensitive or having a narrow therapeutic index

BCRP substrates:	Atorvastatin, fluvastatin, lovastatin, pravastatin, pitavastatin, rosuvastatin, sulfasalazine
P-gp substrates:	dabigatran etexilate, digoxin, fexofenadine, apixaban, rivaroxaban

- Examples of CYP3A4 substrate considered sensitive or having a narrow therapeutics index

CYP3A substrates:	alfentanil, atorvastatin, avanafil, buspirone, conivaptan, darifenacin, darunavir, ebastine, everolimus, fluvastatin, ibrutinib, lomitapide, lovastatin, midazolam, naloxegol, nisoldipine, saquinavir, simvastatin, sirolimus, tacrolimus, tipranavir, triazolam, vardenafil, budesonide, dasatinib, dronedarone, eletriptan, eplerenone, felodipine, indinavir, lurasidone, maraviroc, quetiapine, sildenafil, ticagrelor, tolvaptan

- Example of CYP2D6 substrate with narrow therapeutic index

CYP2D6 substrate:	Thioridazine, atomoxetine, desipramine, dextromethorphan, eliglustat, nebivolol, nortriptyline, perphenazine, tolterodine, R-venlafaxine

- Examples of strong CYP3A4 inhibitor and inducer

Strong CYP3A4 inhibitors:	boceprevir, cobicistat, danoprevir and ritonavir, elvitegravir and ritonavir, grapefruit juice, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, telithromycin, troleandomycin, voriconazole, clarithromycin, idelalisib, nefazodone, nelfinavir
Strong CYP3A inducers:	apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort

See also https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers and https://drug-interactions.medicine.iu.edu/MainTable.aspx and https://crediblemeds.org for a fully updated list of all drugs with known QT risk.

Appendix 3. Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines.
- Applicable International Council of Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines.
- Applicable laws and regulations.

The protocol, protocol amendments, informed consent form (ICF), Investigator Brochure (IB), and other relevant documents (e.g., advertisements) must be submitted to an Institutional Review Boards (IRB)/Independent Ethics Committees (IEC) by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC and regulatory authority approval, when applicable, before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to patients.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the study at the study center and adherence to requirements of 21 *Code of Federal Regulations* (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

After reading the protocol, each Investigator will sign the protocol signature page and send a copy of the signed page to the Sponsor or representative. The study will not start at any study center at which the Investigator has not signed the protocol.

Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing updated information on financial interests during the course of the study and for 1 year after completion of the study.

Insurance

The Sponsor has obtained liability insurance, which covers this study as required by local law and/or national regulations and/or ICH guidelines, whichever is applicable. The terms of the insurance will be kept in the study files.

Informed Consent Process

The Investigator or his/her representative will explain the nature of the study to the patient or his legally authorized representative and answer all questions regarding the study.

Patients must be informed that their participation is voluntary. Patients or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the patient was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the patient or the patient's legally authorized representative.

A patient who is rescreened is not required to sign another ICF if the rescreening occurs within 30 days from the previous ICF signature date.

Data Protection

Patients will be assigned a unique identifier by the Sponsor (or designee). Any patient records or datasets that are transferred to the Sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.

The patient must be informed that his personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

The ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

The Sponsor or its representative will not provide individual genotype results to patients, any insurance company, any employer, their family members, general physician, or any other third party, unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, the Sponsor or representative physician or an Investigator might know a patient's identity and also have access to his or her genetic data. Also, regulatory authorities may require access to the relevant files.

Administrative Structure

The SRC will include, at a minimum, the Sponsor's responsible physician and personnel, as well as selected Principal Investigators. The Principal Investigator and the Sponsor, when appropriate, will invite other specialist individuals to participate in the review, e.g., pharmacokinetic scientists, statisticians, clinical specialists etc.

Medical Monitor

Medical Monitor name and contact information will be provided separately in the Study Contact Sheet.

Dissemination of Clinical Trial Data

The results of the study should be reported within 1 year from the end of the clinical trial. Irrespective of the outcome, the Sponsor will submit to the appropriate database a summary of the results of the clinical trial within 1 year from the end of the clinical trial. It shall be accompanied by a summary written in a manner that is understandable to laypersons (where applicable).

Data Quality Assurance

All patient data relating to the study will be recorded in printed or electronic case report forms (eCRFs) unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized study center personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Source Documents

The Investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the study center's patients. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail).

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's study center.

Data reported in the eCRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in Clinical Monitoring Plan.

Study and Study Center Closure

The Sponsor designee reserves the right to close the study center or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study centers will be closed upon study completion. A study center is considered closed when all required documents and study supplies have been collected and a study center closure visit has been performed.

The Investigator may initiate study center closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study center by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of patients by the Investigator.
- Discontinuation of further study treatment development.

Publication Policy

The data generated by this study are confidential information of the Sponsor. The publication policy with respect to the Investigator and study center will be set forth in the Clinical Trial Agreement.

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual study center data. In this case, a Coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Sponsor will base its publication policy on a number of key factors that include: intellectual input into the protocol design, analysis of data and patient enrollment. Sponsor is committed to a fair and equitable determination of the various publication roles such as lead author and senior author on future manuscripts and abstracts/presentations.

Appendix 4. Clinical Laboratory Tests

The tests detailed in Table 14 will be performed by the local laboratory. The results of each test must be entered into the eCRF. Investigators must document their review of each laboratory safety report.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 14. Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters	
Hematology	Platelet count	White blood cell count with differential:
	Red blood cell count	• Absolute neutrophils
	Hemoglobin	• Absolute lymphocytes
	Hematocrit	• Absolute monocytes
	White blood cells	• Absolute eosinophils
		• Absolute basophils
Clinical chemistry	Blood urea nitrogen (BUN) or urea	Aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase (SGOT)
	Creatinine	Alanine aminotransferase (ALT)/serum glutamic-pyruvic transaminase (SGPT)
	Glucose (non-fasting)	Alkaline phosphatase (ALP)
	Magnesium	Creatine kinase
	Potassium	Creatine kinase myocardial band (MB) fraction will be performed if clinically indicated
	Sodium	Chloride
	Total calcium	Amylase
	Lactate dehydrogenase	Total bilirubin
	Albumin	Direct, conjugated, and unconjugated bilirubin will be performed if clinically indicated [a]
	Uric acid	Total protein
	C-reactive protein	Phosphorus or phosphate
		Carbon dioxide (bicarbonate)
Coagulation	International normalized ratio (INR)	Partial thromboplastin time (PTT)
	Prothrombin time (PT) (optional)	Activated partial thromboplastin time (APTT)
Urinalysis [b]	Leucocyte esterase	pH
	Protein	Nitrites
	Urine bilirubin	Specific gravity
	Urobilinogen	Glucose (qual)
	Ketones	Blood (qual)
	Microscopy [c] (if clinically indicated)	

Laboratory Assessments	Parameters
Viral serology [d]	HIV I and II Hepatitis C virus Hepatitis B virus
Thyroid profile	Thyroid-stimulating hormone (TSH)
Other tests	Prostate-specific antigen (PSA), tumor, bone, and soft tissue assessments (see the Schedule of Activities [Section 3] for more information). Serum testosterone using ultrasensitive testosterone assays with a sensitivity to 1 to 2 ng/dL.

Note: There is no need to repeat hematology, coagulation, and urinalysis on C1D1 if baseline assessment is performed within 72 hours prior to that date. For blood chemistry and urinalysis, there is no need to repeat on C1D1 if baseline assessment is performed within 7 days prior to C1D1. Details of dosage modification, stopping criteria, and follow-up of abnormal test results are provided in Sections 8.2.1.1, 9.1, and 10.2.

a Unconjugated bilirubin can be derived from total and conjugated bilirubin.
b Urine dipstick testing is acceptable at the Screening and End of Study visits.
c Only if urine dipstick is positive for blood, protein, nitrates, or leukocyte esterase.
d Historical results obtained within 30 days of enrollment may be used to determine eligibility.

Appendix 5. Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of Adverse Event (AE)

AE Definition
• An adverse event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a clinical investigation patient administered study drug and that does not necessarily have a causal relationship with this treatment. • An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study drug, whether or not considered related to the study drug.

Definition of Serious Adverse Event (SAE)

An SAE is defined as any untoward medical occurrence that, at any dose:
a) Results in death
b) Is life-threatening The term "life-threatening" is defined as an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c) Requires inpatient hospitalization or causes prolongation of existing hospitalization The following hospitalizations are not considered SAEs in this clinical study: • a visit to the emergency room or other department for <24 hours, that does not result in admission (unless it meets criteria for an important medical or life-threatening event); • elective surgery planned prior to signing consent; • admissions as per protocol for a planned medical/surgical procedure; • routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy); • medical/surgical admission other than to remedy ill health and planned prior to entry on the study; • admission encountered for another life circumstance that has no bearing on health status and requires no medical or surgical intervention (e.g., lack of housing, caregiver respite, administrative reason); and • admission for anticancer therapy in the absence of any other SAEs.
d) Results in persistent disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions.
e) Is a congenital anomaly/birth defect
f) Is an Important Medical Event An Important Medical Event is defined as a medical event that may not be immediately life-threatening or result in death or hospitalization but, based on appropriate medical and scientific judgment, may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization. Potential drug-induced liver injury (DILI) is also considered an important medical event.

Recording and Follow-up of AE and/or SAE During Study (up to notice from Sponsor of primary study completion)

AE and SAE Recording During Study

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the eCRF. Each event must be recorded separately.
- It is not acceptable for the Investigator to send photocopies of the patient's medical records to the Sponsor in lieu of completion of the AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before submission to the Sponsor.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Severity

- The Investigator will make an assessment of the severity for each AE and SAE reported during the study according to NCI CTCAE version 5.

Assessment of Causality

The causal relationship to the study drugs is determined by a physician and should be used to assess all AEs. The causal relationship can be one of the following:

- Related: There is a reasonable causal relationship between study drug administration add the AE.
- Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" indicates there is evidence to imply a causal relationship.

Follow-up of AEs and SAEs

- If only limited information is initially available, follow-up reports are required and must include the same Investigator term(s) as the initial report.
- If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, the SAE report must be updated and submitted within 24 hours of becoming aware of the new information.
- All treatment-related AEs and SAEs must be followed to resolution or stabilization.

Reporting of SAEs During Study (up to notice from Sponsor of primary study completion)

SAE Reporting During Study

The Investigator must report all SAEs within 24 hours of the Investigator's discovery. The primary method of SAE reporting is via the study eCRF system. If timely reporting is not possible through the eCRF, back-up methods are below:

For North America:
Attention: Arvinas Safety
E-mail: pvintake@arvinas.com
Fax number: 1-888-887-8097

For Europe:
Attention: Arvinas Safety
E-mail: pvintake@arvinas.com
Fax number: +44 1628 540028

The Arvinas safety team (or delegate) will contact the Investigator via telephone or by e-mail for follow-up information regarding the SAE, as appropriate.
The Investigator, or designated party, should notify the appropriate IRB/IEC of SAEs occurring at the study site and other AE reports received from the Sponsor, in accordance with local procedures and statutes.

Reporting of SAEs, Deaths Due to Disease Progression, and AEs Leading to Discontinuation of Study Drug After Notice From Sponsor of Primary Study Completion

SAE Reporting and Reporting of Deaths Due to Disease Progression and AEs Leading to Discontinuation of Study Drug After Notice From Sponsor of Primary Study Completion

After notice from Sponsor of primary study, SAEs, deaths due to disease progression and AEs leading to discontinuation of study drug will no longer be collected via the eCRF. However, for patients remaining on investigational treatment and in safety follow-up, the Investigator must report to the Sponsor:

- All SAEs within 24 hours of the Investigator's discovery via paper form submission.
- All deaths due to disease progression and AEs leading to discontinuation of study drug, within 10 days via paper form submission.

After notice from Sponsor of primary study completion and notification of database lock from the Sponsor, the primary method of reporting is via paper:

For North America:
Attention: Arvinas Safety
E-mail: pvintake@arvinas.com
Fax number: 1-888-887-8097

For Europe:
Attention: Arvinas Safety
E-mail: pvintake@arvinas.com
Fax number: +44 1628 540028

The Arvinas safety team (or delegate) will contact the Investigator via telephone or by e-mail for follow-up information regarding SAEs, deaths due to disease progression and AEs leading to discontinuation of study drug, as appropriate.

The Investigator, or designated party, should notify the appropriate IRB/IEC of SAEs occurring at the study site and other AE reports received from the Sponsor, in accordance with local procedures and statutes.

National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0

https://evs.nci.nih.gov/ftp1/CTCAE/About.html

Appendix 6. Contraceptive Guidance and Collection of Pregnancy Information

Contraception Guidance

Male patients with female partners of childbearing potential are eligible to participate if they agree to ONE of the following during the protocol-defined time frame:

- Remain abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a longterm and persistent basis) and agree to remain abstinent.
- Use a male condom and have their partner use of a contraceptive method with a failure rate of <1% per year as described in Table 15 when having penile-vaginal intercourse with a woman of childbearing potential (WOCBP) who is not currently pregnant.

ARV-110 has a long effective clinical half-life of approximately 93 hours as calculated for the 420 mg daily dose. Based on 5 half-lives for washout (19 days) plus 90 days (109 days total) for the sperm cycle per Clinical Trials Facilitation and Coordination (CTFG) contraception guidance, males with reproduction potential who are sexually active should use highly effective contraception (unless confirmed prior castration) during treatment with ARV-110 and for at least 16 weeks after the last dose of ARV-110. Additionally, they should refrain from donating sperm for the duration of the study and for at least 16 weeks after the last dose of ARV-110.

Male patients with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration for the duration of the study and for at least 16 weeks after the last dose of study drug.

Table 15. Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User-Dependent [a] Failure rate of <1% per year when used consistently and correctly.
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • Oral • Intravaginal • Transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User-Independent [a]
Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • Intrauterine device • Intrauterine hormone-releasing system • Bilateral tubal occlusion
Vasectomized partner A vasectomized partner is a highly effective birth control method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the patient.

a Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for patients in clinical studies.

Collection of Pregnancy Information

Male patients with partners who become pregnant

The Investigator will attempt to collect pregnancy information on any male patient's female partner who becomes pregnant while the male patient is in this study. This applies only to male patients who receive ARV-110.

After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Appendix 7. RECIST 1.1 and PCWG3 Criteria

The antitumor activity of ARV-110 will be assessed using the Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1) with modification recommended by the Prostate Cancer Working Group 3 (PCWG3) criteria. The RECIST 1.1 and PCWG3 criteria outlined here are adapted from Eisenhauer et al. (2009) and Scher et al. (2016).

PCWG3 advises following RECIST 1.1 for extra-skeletal disease but recommends that up to 5 lesions per site of metastatic spread (e.g., lung, liver, lymph nodes as separate sites) be recorded to address disease heterogeneity and to track patterns of metastatic progression. Bone lesions (assess by PCWG3 criteria) should be recorded separately.

Categorizing Lesions at Baseline

Measurable Lesions: **Lesions that can be accurately measured in at least 1 dimension.**

- Lesions with longest diameter twice the slice thickness and ≥10 mm when assessed by computed tomography (CT) or magnetic resonance imaging (MRI) (slice thickness of 5 to 8 mm). Record individual sites of spread (lung, liver, adrenal, central nervous system) separately; up to 5 lesions per site.
- Malignant lymph nodes with the short axis ≥15 mm when assessed by CT or MRI. Nodes ≥1.5 cm in the short axis are considered measurable; nodes ≥1.0 and less than 1.5 cm in the short axis are considered pathologic according to clinical discretion, and nontarget; nodes <1.0 cm in the short axis are non-pathologic. Record pelvis and extra-pelvis (retroperitonea, mediastinal, thoracic, other) nodal disease separately; up to 5 nodes in total.

NOTE: The shortest axis is used as the diameter for malignant lymph nodes, longest axis for all other measurable lesions.

Non-measurable Disease

Non-measurable disease includes lesions too small to be considered measurable (including nodes with short axis between 10 and 14.9 mm) and truly non-measurable disease such as pleural or pericardial effusions, ascites, inflammatory breast disease, leptomeningeal disease, and lymphangitic involvement of skin or lung.

- Previous local treatment: A previously irradiated lesion (or lesion subjected to other local treatment) is nonmeasurable unless it has progressed since completion of treatment.

Normal Sites

- Cystic lesions**:** Simple cysts should not be considered as malignant lesions and should not be recorded either as target or nontarget disease. Cystic lesions thought to represent cystic metastases can be measurable lesions if they meet the specific definition above. If noncystic lesions are also present, these are preferred as target lesions.
- Normal nodes: Nodes with short axis <10 mm are considered normal and should not be recorded or followed either as measurable or nonmeasurable disease.

Recording Tumor Assessments

All sites of disease must be assessed at baseline. Baseline assessments should be done as close as possible prior to study start. For an adequate baseline assessment, all required scans must be done within 28 days prior to treatment and all disease must be documented appropriately. If baseline assessment is inadequate, subsequent statuses generally should be indeterminate.

Target Lesions

All measurable lesions up to a maximum of 5 lesions per site, and 5 lymphatic lesions in total, representative of all involved organs, should be identified as target lesions at baseline. Target lesions should be selected on the basis of size (longest lesions) and suitability for accurate repeated measurements. Record the longest diameter for each lesion, except in the case of pathological lymph nodes for which the short axis should be recorded. The sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions at baseline will be the basis for comparison to assessments performed on study.

- If 2 target lesions coalesce the measurement of the coalesced mass is used. If a large target lesion splits, the sum of the parts is used.
- Measurements for target lesions that become small should continue to be recorded. If a target lesion becomes too small to measure, 0 mm should be recorded if the lesion is considered to have disappeared; otherwise, a default value of 5 mm should be recorded.

NOTE: When nodal lesions decrease to <10 mm (normal), the actual measurement should still be recorded.

Non-target Disease

All non-measurable disease is non-target. All measurable lesions not identified as target lesions are also included as non-target disease. Measurements are not required but rather tumor status will be expressed as Absent, Indeterminate/Inevaluable, Present/Not Increased, or Increased.

Objective Response Status at Each Evaluation

Disease sites must be assessed using the same technique as baseline, including consistent imaging modality, administration of contrast and timing of scanning. If a change needs to be made the case must be discussed with the radiologist to determine if substitution is possible. If not, subsequent objective statuses are indeterminate.

Target Disease

- Complete response (CR): Complete disappearance of all target lesions with the exception of nodal disease. All target nodes must decrease to normal size (short axis <10 mm). All target lesions must be assessed.

- Partial response (PR): Greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. The short diameter is used in the sum for target nodes, while the longest diameter is used in the sum for all other target lesions. All target lesions must be assessed.
- Stable: Does not qualify for CR, PR, or disease progression. All target lesions must be assessed. Stable can follow PR only in the rare case that the sum increases by <20% from the nadir, but enough that a previously documented 30% decrease no longer holds.
- Objective progression: 20% increase in the sum of diameters of target measurable lesions above the smallest sum observed (over baseline if no decrease in the sum is observed during therapy), with a minimum absolute increase of 5 mm.
- Indeterminate: Progression has not been documented, and:
  - One or more target measurable lesions have not been assessed; OR
  - Assessment methods used were inconsistent with those used at baseline; OR
  - One or more target lesions cannot be measured accurately (e.g., poorly visible unless due to being too small to measure); OR
  - One or more target lesions were excised or irradiated and have not reappeared or increased.

Non-target Disease

- Complete response (CR): Disappearance of all nontarget lesions and normalization of tumor marker levels. All lymph nodes must be "normal" in size (<10 mm short axis).
- NonCR/Nondisease progression: Persistence of any nontarget lesions and/or tumor marker level above the normal limits.
  - Disease progression: Unequivocal progression of pre-existing lesions. **Generally, the overall tumor burden must increase sufficiently to merit discontinuation of therapy**. In the presence of stable disease or PR in target disease, progression due to unequivocal increase in non-target disease should be rare.
  - Indeterminate: Progression has not been determined and 1 or more non-target sites were not assessed, or assessment methods were inconsistent with those used at baseline.

New Lesions

The appearance of any new unequivocal malignant lesion indicates disease progression. If a new lesion is equivocal, for example due to its small size, continued assessment will clarify the etiology. If repeat assessments confirm the lesion, then progression should be recorded on the date of the initial assessment. A lesion identified in an area not previously scanned will be considered a new lesion.

Record all new lesions and the sites of all new lesions.

Supplemental Investigations

- If CR determination depends on a residual lesion that decreased in size but did not disappear completely, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate. If no disease is identified, objective status is CR.
- If progression determination depends on a lesion with an increase possibly due to necrosis, the lesion may be investigated with biopsy or fine needle aspirate to clarify status.

Subjective Progression

Patients requiring discontinuation of treatment without objective evidence of disease progression should not be reported as disease progression on tumor assessment eCRFs. This should be indicated on the EOT eCRF as off-treatment due to clinical deterioration of health status or worsening. Every effort should be made to document objective progression even after discontinuation of treatment.

Assessment of Radiographic Response and Progression in Patients with Metastatic Castration-Resistant Prostate Cancer

Radiographic imaging for patients with CRPC is categorized as soft tissue or bone. Soft tissue imaging may include CT scans of the chest, abdomen and pelvis or MRIs of the abdomen and pelvis. Bone imaging must be whole-body radionuclide bone scan.

The Investigator will assess response of soft tissue disease as described above. However, bone disease is not to be considered as RECIST 1.1 non-target lesions.

Criteria for Evidence of Radiographic Progression

Bone disease will be assessed for progressive disease only by the PCWG3. The documentation required for the determination of radiographic progression is shown in Table 16.

Table 16. Determination of Radiographic Progression

Date Progression Detected [a]	Criteria for Progression	Criteria to Confirm Progression	Criteria to Document Disease Progression on Confirmatory Scan
Week 8	Bone lesions: 2 or more new lesions compared to screening bone scan by PCWG3	Timing: At least 6 weeks after progression identified or at Week 16 visit [b]	Two or more new bone lesions on bone scan compared to Week 8 scan
	Soft tissue lesions: Progressive disease on CT or MRI by RECIST 1.1	No confirmatory scan required for soft tissue disease progression	No confirmatory scan required for soft tissue disease progression
Week 16 or later	Bone lesions: 2 or more new lesions on bone scan compared to Week 8 bone scan	Timing: At least 6 weeks after progression identified or at next imaging time point [b]	Persistent or increase in number of bone lesions on bone scan compared to prior scan [c]
	Soft tissue lesions: Progressive disease on CT or MRI by RECIST 1.1	No confirmatory scan required for soft tissue disease progression	No confirmatory scan required for soft tissue disease progression

Abbreviations: CT=computed tomography; MRI=magnetic resonance imaging; PCWG3=Prostate Cancer Working Group 3; RECIST=Response Evaluation Criteria in Solid Tumors.

a Progression detected by bone scan at an unscheduled visit either before Week 8 or between scheduled visits will require a confirmatory scan at least 6 weeks later and should follow confirmation criteria outlined in the table for the next scheduled scan.

b Confirmation must occur at the next available scan.

c For confirmation, at least 2 of the lesions first identified as new must be present at the next available scan (confirmation scan).

Disease progression in bone must be confirmed at least 6 weeks later, as per PCWG3. See Table 17 for the timing of confirmatory imaging requirements.

Table 17. Confirmatory Imaging Requirements for Patients with CRPC Based on RECIST 1.1 and PCWG3

Disease Site	Response	Progression [a]
Soft tissue	Recommended to be confirmed at least 4 weeks later	No confirmation required
Bone	Not applicable	Must be confirmed at least 6 weeks later

Abbreviations: CRPC=castrate-resistant prostate cancer; PCWG3=Prostate Cancer Working Group 3; RECIST= Response Evaluation Criteria in Solid Tumors.

a To inform permanent treatment discontinuation.

Table 18. RECIST 1.1 Objective Response Status at Each Evaluation

Target Lesions	Non-target Disease	New Lesions	Objective Status
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Indeterminate or Missing	No	PR
PR	Non-CR/Non-PD, Indeterminate, or Missing	No	PR
SD	Non-CR/Non-PD, Indeterminate, or Missing	No	SD
Indeterminate or Missing	Non-PD	No	Indeterminate
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR=complete response; PD=progressive disease; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors; SD=stable disease.

Table 19. RECIST 1.1 Objective Response Status at Each Evaluation for Patients with Non-Target Disease Only

Non-target Disease	New Lesions	Objective Status
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
Indeterminate	No	Indeterminate
Unequivocal progression	Yes or No	PD
Any	Yes	PD

Abbreviations: CR=complete response; PD=progressive disease; RECIST=Response Evaluation Criteria in Solid Tumors.

Procedures for Assessing PSA Response/Progression Following Study Treatment

Increases and decreases in PSA will be tracked in order to assess disease response. The PSA readings on their own will not be used to define progression for purposes of treatment discontinuation in this protocol. PSA response and PSA progression will be defined according to the consensus guidelines of the PCWG3:

- PSA partial response is defined as a ≥50% decline in PSA from Cycle 1 Day 1 PSA value. This PSA decline must be confirmed to be sustained by a second PSA value obtained 3 or more weeks later.
- PSA progression date is defined as the date that a ≥25% increase and an absolute increase of ≥2 ng/mL above the nadir is documented, which is confirmed by a second consecutive value obtained 3 or more weeks later.

PCWG3 Bone Progression Criteria

Figure 4 depicts an optional bone scan assessment tool (Dennis, 2011).

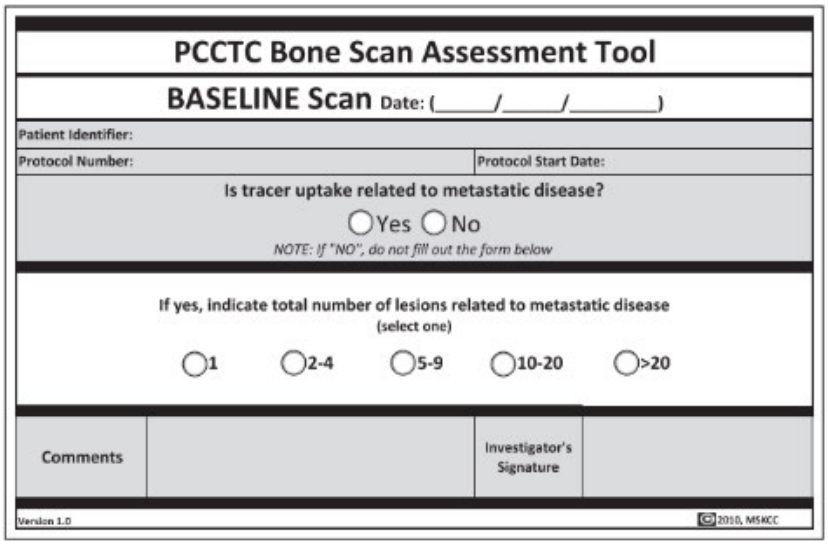
A patient will be considered to have progressed on bone scan based on the PCWG3 criteria in Table 20:

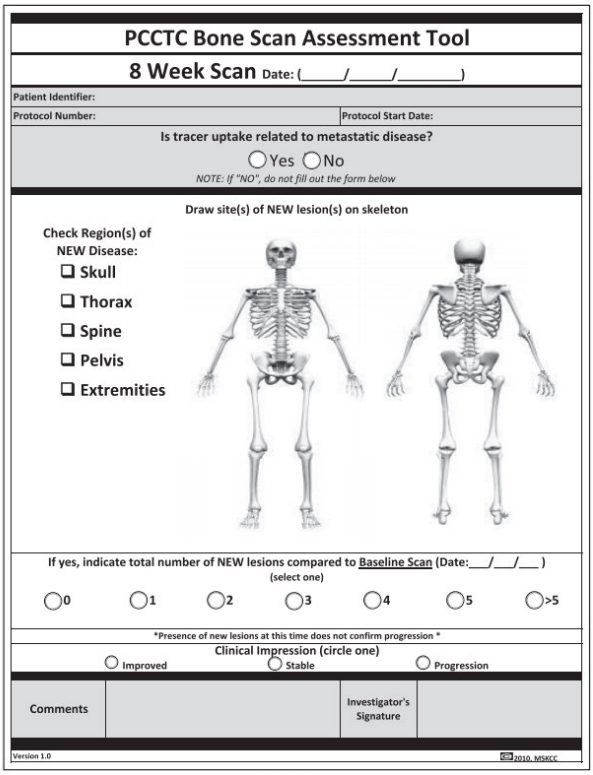
Table 20. Radiological Criteria for Ascribing Disease Progression

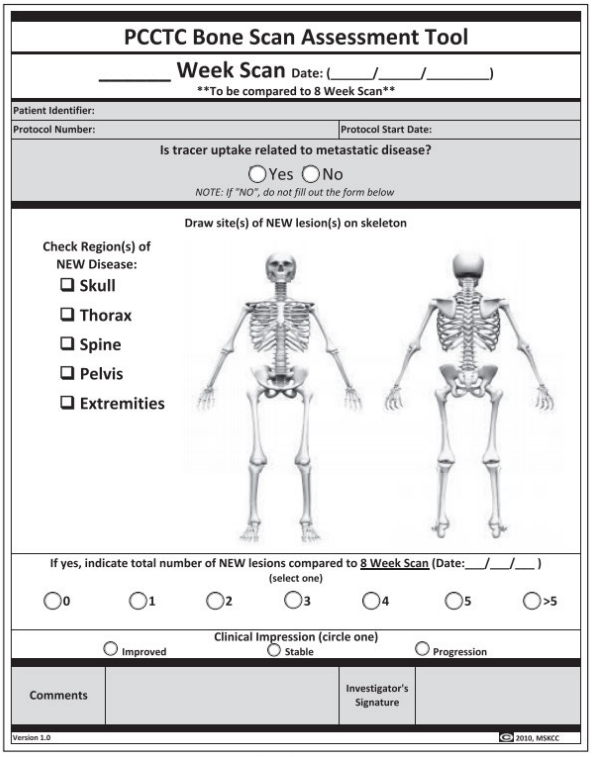
Evidence of Progression	Confirmation	Action
Bone Disease: At least **2 new lesions on first post-treatment scan**, with at least 2 additional lesions on the next scan (2+2 rule).	Confirmatory scan (performed 6 or more weeks later) should show an additional 2 new lesions compared to the first post-treatment scan (i.e., a total of ≥4 new lesions compared with the baseline bone scan). The date of progression is the date of the first post-treatment scan, when the first two new lesions were documented.	Investigators are highly encouraged to maintain the patient's treatment with study medication unless progression is confirmed.
Bone Disease: For scans **after the first post-treatment scan**, at least 2 new lesions relative to the first post-treatment scan confirmed on a subsequent scan.	Confirmatory scan (performed 6 or more weeks later) should confirm the presence of the 2 new lesions compared to the first post-treatment scan. The date of progression is the date of the scan that first documents the second lesion.	Investigators are highly encouraged to maintain the patient's treatment with study medication unless progression is confirmed.
Soft Tissue Disease as defined by RECIST on CT/MRI.	Progression at any scheduled reassessment ≥12 weeks does not need to be confirmed.	Investigators are highly encouraged to maintain the patient's treatment with study medication unless radiological progression is observed.

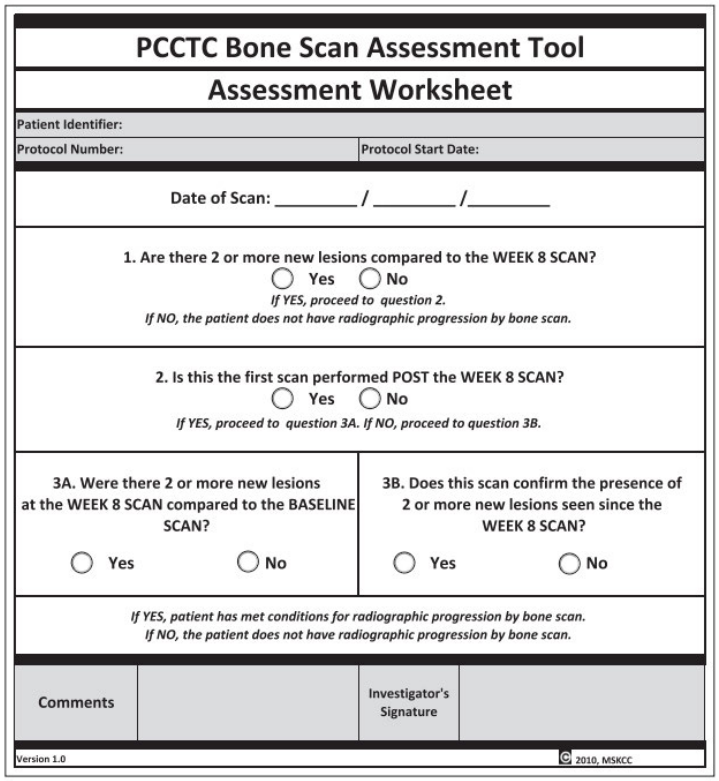
Abbreviations: CT=computed tomography; MRI=magnetic resonance imaging; RECIST= Response Evaluation Criteria in Solid Tumors.
NOTE: Patients who have evidence of radiographic disease progression may be considered for continued study therapy provided the Principal Investigator has determined that they are still benefiting from study therapy. All such requests must be reviewed and approved by the Arvinas' Medical Monitor.

Figure 4. Bone Scan Assessment Tool









PCCTC Bone Scan Assessment Tool

Assessment Worksheet

Patient Identifier:	
Protocol Number:	Protocol Start Date:

Date of Scan: _____ / _____ /_____

1. Are there 2 or more new lesions compared to the WEEK 8 SCAN?
◯ Yes ◯ No
If YES, proceed to question 2.
If NO, the patient does not have radiographic progression by bone scan.

2. Is this the first scan performed POST the WEEK 8 SCAN?
◯ Yes ◯ No
If YES, proceed to question 3A. If NO, proceed to question 3B.

3A. Were there 2 or more new lesions at the WEEK 8 SCAN compared to the BASELINE SCAN?	3B. Does this scan confirm the presence of 2 or more new lesions seen since the WEEK 8 SCAN?
◯ Yes ◯ No	◯ Yes ◯ No

If YES, patient has met conditions for radiographic progression by bone scan.
If NO, the patient does not have radiographic progression by bone scan.

Comments		Investigator's Signature	

Version 1.0 © 2010, MSKCC

Source: http://ascopubs.org/doi/figure/10.1200/JCO.2015.64.2702

Appendix 8. Eastern Cooperative Oncology Group (ECOG) Performance Status

ECOG Performance Status

Developed by the Eastern Cooperative Oncology Group, Robert L. Comis, MD, Group Chair *

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

* Oken et al. (1982).

Appendix 9. COVID-Related Guidelines

Please also refer to FDA Guidance: https://www.fda.gov/media/136238/download

Guidance for COVID-19 Vaccine Administration

- **For patients who have not initiated study treatment:**

It is recommended that patients should receive the second dose of vaccine at least 5 days prior to initiation of study treatment. In addition, patients should have completely recovered from any side effects related to administration of the vaccine before starting study treatment.

- **For patients already on study treatment and beyond Cycle 1:**

Patients who are already receiving study treatment and beyond Cycle 1, may receive the vaccine as it becomes available to them. Please carefully document any AEs that occur related to the vaccine administration and advise the Sponsor of any significant reactions that occur.

TeleMed Visit Guidance and Accepted Use

The use of Video TeleMed Visits during the COVID-19 pandemic will be acceptable in the following cases:

- Visits where only AE assessment and routine blood samples, which may be performed locally, are required and the results are received and reviewed by the Investigator prior to the TeleMed visit with the patient.
- Visits occurring on Day 15 of Cycle 2 and beyond may be done via TeleMed if the patient did not have any significant toxicities requiring reassessment at the previous in-person Day 1 visit and has not reported any new significant toxicity in the interim. The same requirement for receiving and reviewing laboratory results as noted in the previous bullet point also apply in this case.
- Other study visits should be maintained as in-person clinic visits unless local, governmental, or other restrictions are in place that prohibit travel or in-person clinic visits. In such cases, the Sponsor should be advised in advance, where possible, that a TeleMed visit will be used.
- The use of alternate or local labs and/or imaging centers is allowed at the discretion of the Investigator. Use of an alternate imaging center should have Sponsor approval prior to use.

Shipment of Drug Supply Based on COVID-related Limitations

Patients who cannot be seen in clinic due to quarantine requirements or other limitations due to COVID-19 restrictions may receive oral IP shipped, utilizing a secure delivery method with signature required, directly to their home address. The site is to confirm receipt of the shipment with the patient, document patient compliance and the need for direct shipment to the patient.

Positive COVID-19 Test

A positive COVID-19 test will not require a dose interruption. Any dose interruption should be based on the severity of any associated symptoms, the type of COVID-19 treatment needed, and the Investigator's judgment. If dosing is interrupted, dosing may resume without dose modification and based on Investigator's judgment. The Medical Monitor or Designee should be notified if treatment other than OTC medications for COVID-19 is needed or there is treatment interruption due to COVID-19.

Treatment for COVID-19 While On Study

Treatment for COVID-19 is permitted, however, DDIs with study medication must be considered. The Medical Monitor or Designee should be notified if treatment of COVID-19 is needed with medications other than OTC treatments or there is treatment interruption due to COVID-19. Clear documentation must be provided in the patient's medical record and their eCRF regarding all therapy received as well as all AEs related to COVID-19 and its treatment.

Appendix 10. Important Information and Mapping Table for Amendment 3 and Patients Remaining on Treatment After Notice From Sponsor of Primary Study Completion

Section Number	Notes
Global	After notice from Sponsor of primary study completion, clinical data will no longer be recorded in the eCRF.
3 Schedule of Activities	Clarification added to Table 2 regarding EOT for those patients on treatment after notice from Sponsor of primary study completion. New Table 5 is only applicable once Amendment 3 is approved, and after notice from Sponsor of primary study completion (i.e., all patients have received 9 or more months of treatment).
6.7 Rationale for Patients Continuing on Treatment after Notice from Sponsor of Primary Study Completion	New Section 6.7 providing rationale for patient continuing on treatment after notice from Sponsor of primary study completion.
8.2 Treatments Administered	New Section 8.2.1.1 provides clarification on method of treatment assignment for ongoing patients after notice from Sponsor of primary study completion.
8.3 Treatment Modifications and Discontinuations	Applicable as is. Note that the sponsor is available to be notified of treatment modifications and discontinuations; refer to the Study Contact Sheet.
8.4 Preparation/Handling/Storage/Accountability	Applicable as is. Also see updated Pharmacy Manual.
8.6 Treatment Compliance	For additional guidance specific to compliance for ongoing patients, see Section 8.6.1.
8.8 Treatment After the End of the Study	For additional guidance specific to End of Study, see added language in Section 8.8.

10 Study Assessments and Procedures	In general, Section 10 subsections are applicable only for assessments described in the SoA, Table 5. For Section 10.1.4 (Clinical Safety Laboratory Assessments), note that the sponsor should be notified if clinical safety laboratory assessments reveal an SAE or AE leading to discontinuation of study drug; refer to Section 10.2.1.1 and the Study Contact Sheet. In Section 10.2 (Adverse Events), alternate instructions are provided in Section 10.2.1.1 for Alternate Collection and Reporting of SAEs, Deaths Due to Disease Progression and AEs Leading to Discontinuation of Study Drug after Notice from Sponsor of Primary Study Completion.
12 Safety Review Committee	Clarification added for SRC meetings.
14 Appendices	In general, Appendices are applicable only for relevant assessments described in the SoA, Table 5; i.e., Appendix 1, Appendix 2, Appendix 3, Appendix 5,Appendix 6, and Appendix 9 may still be applicable. In Appendix 5, revised reporting instructions are provided under Reporting of SAEs, Deaths Due to Disease Progression, and AEs Leading to Discontinuation of Study Drug After Notice From Sponsor of Primary Study Completion.

Appendix 11. Signature Page

Investigator Acknowledgment

PROTOCOL TITLE: A Phase 1b open-label clinical trial to evaluate the safety, tolerability, and pharmacokinetics of ARV-110 in combination with abiraterone in patients with metastatic prostate cancer

PROTOCOL NO: ARV-110-mCRPC-103

VERSION: Amendment 3.0; 28 March 2024

This protocol is a confidential communication of Arvinas Androgen Receptor, Inc. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from the Sponsor.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the study center in which the study will be conducted. Return the signed copy to Arvinas Androgen Receptor, Inc.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center:

_____

_____

_____

_____

Signature Page for VV-CLIN-000054 v3.0

Approval	[redacted] Clinical 28-Mar-2024 13:31:32 GMT+0000

Signature Page for VV-CLIN-000054 v3.0