Statistical Analysis Plan (SAP)

Protocol Title:	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
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1.0 Approvals

Sponsor	
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(NOTE: Electronic Signatures sh

2.0 Change History

Version/Date	Change Log
1.0 / 07Oct2023	Created as new
1.1 / 31May2024	Updated per a few minor comments from Arvinas
2.0 / 09SEP2024	Updated per dry run comments from Arvinas

3.0 Table of Contents

4.0 Purpose

The Statistical Analysis Plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under Arvinas Inc. Protocol ARV-110-mCRPC-103, Amendment 2.

5.0 Scope

This SAP describes the methods to be used during the reporting and analyses of data collected in Arvinas. Inc. Protocol ARV-110- mCRPC-103, titled “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”.

The Statistical Analysis Plan outlines the following:

- Study Objectives
- Study Design
- Study Endpoints
- Applicable Study Definitions
- Statistical Methods

6.0 Introduction

The study protocol provides conduct for a Phase 1b open-label study to evaluate the safety, tolerability, and pharmacokinetics of ARV-110 in combination with abiraterone in patients with metastatic prostate cancer.

This SAP should be read in conjunction with the study protocol and case report forms (CRFs).

Changes made to the SAP after it has been approved but prior to final analyses of data will be documented in amendment(s). Important changes to the SAP, along with the justification for the changes, will be described in the clinical study report (CSR). Changes to the protocol will require a SAP amendment ONLY if the changes are to a principal feature of the protocol.

6.1 Changes from Protocol

6.1.1 Analysis Sets

Section 11.2.1 of the Protocol specifies the definition of the Enrolled Analysis Set as “…successfully undergone the inclusion/exclusion assessment”. This has been removed from the SAP definition after discussion with the sponsor, on the basis that completing the eligibility assessment should not imply passing eligibility criteria. This analysis set will be all patients consenting to participate, including screen failures. This is described in Section 0 of the SAP.

Section 11.2.2 of the Protocol specifies the definition of the Safety Analysis Set. As some components of efficacy will use this analysis set, it was decided to rename this as the All-Treated Set, to avoid confusion when overlapping with efficacy. This is described in Section 0 of the SAP.

7.0 Study Objectives

The objectives of the study and its corresponding endpoints are as follows:

Objectives	Endpoint
Primary	
• To evaluate the safety and tolerability of ARV-110 in combination with abiraterone and select the RP2D/schedule for the combination	• DLTs in first 4 weeks of the study combination treatment and determination of the RP2D • Adverse events (AEs) as characterized by type, frequency, severity (as graded by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (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: AUCtau, AUClast, Cmax, Cmin, Tmax, Clast, and Tlast.
• To assess preliminary antitumor activity	• Anti-tumor activity of ARV-110 in combination with abiraterone will be assessed by evaluating the following: o Percent of patients with lack of PSA progression o A ≥30% or ≥50% decline in PSA from Cycle 1 Day 1 (baseline) PSA value (PSA30 and PSA50, respectively) response rate and duration o Time to PSA progression o Radiographic progression-free survival (rPFS) o Overall response rate (ORR) per modified Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1/PCGW3 and duration of response (DOR) in patients with measurable disease at baseline

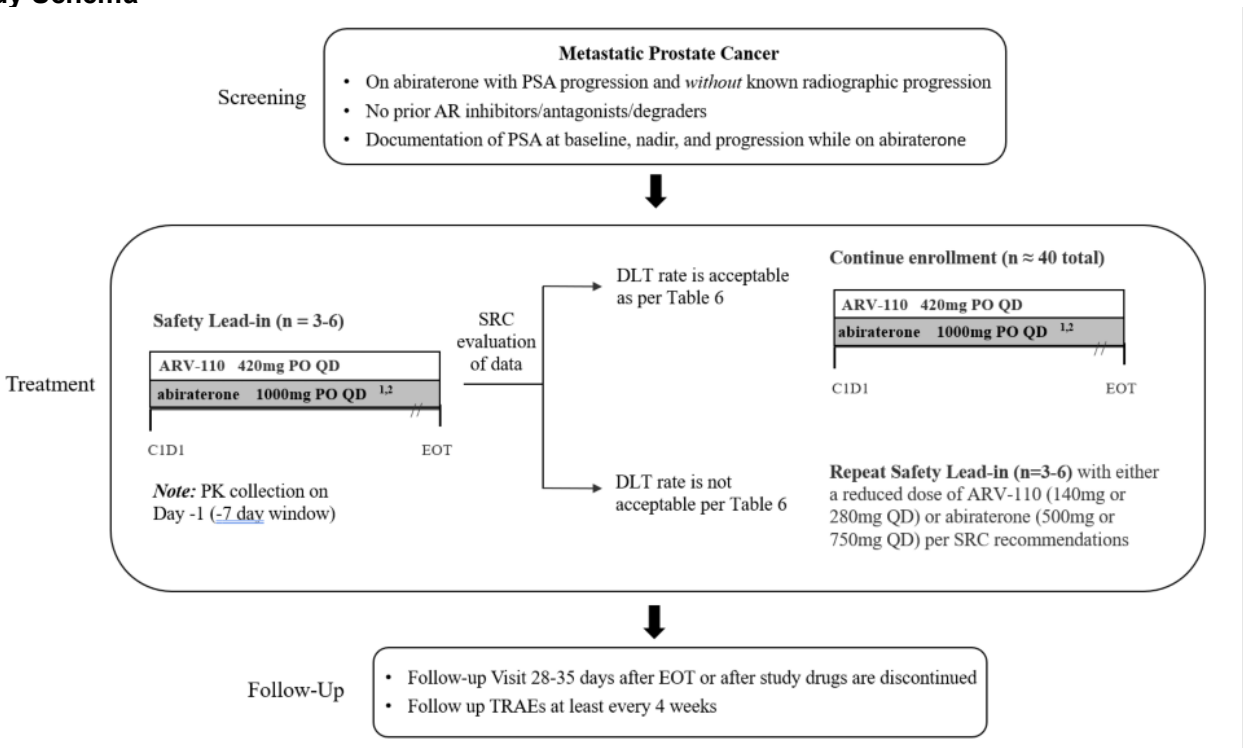
Exploratory	
[redacted]	

8.0 Study 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 metastatic prostate cancer (mPC) who have rising prostate-specific antigens (PSAs) (without known radiographic disease progression), while receiving abiraterone with a concomitant corticosteroid. The study design has accounted for potential drug-drug interactions (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).

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 PK and safety data.

8.1 Sample Size Considerations

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% confidence intervals (CIs) per the Clopper-Pearson exact method (Clopper CJ & Pearson ES, 1934) will be 0.21 to 0.33. Details are provided 15.4 Appendix 4 . Patients whose baseline scans show radiographic progression (compared to the last scans obtained prior to study enrollment) and/or not clinically benefitting from abiraterone at the time of consent may be replaced to ensure a minimum of 40 study patients with PSA-only progression on abiraterone at study entry.

8.2 Randomization

Not applicable as this is a non-randomized study.

9.0 Analysis Sets

9.1 Enrolled Analysis Set

The Enrolled analysis set consists of patients who are registered to participate in this study with informed consent signed.

9.2 All-Treated Analysis Set

The All-Treated analysis set consists of enrolled patients receiving any amount of study drug (ARV-110 dose or abiraterone) after and including Day 1 Cycle 1. The All-Treated 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 All-Treated analysis set.

9.3 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.

9.4 Pharmacokinetic Analysis Set

The PK data analysis set will include all patients who have received at least 1 dose of ARV-110 or 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 ARV-110 which would lead to exclusion(s). For parameter calculations, when intensive sampling was collected, patients who receive study drug and have sufficient PK data to provide at least one PK exposure endpoint at minimum, and had no protocol deviations affecting the validity of the PK data nor were excluded will be included in the PK analysis set.

9.5 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.

9.6 Response Efficacy Analysis Set

The Response Efficacy analysis set will be comprised of all patients treated with both ARV-110 and abiraterone in the All-Treated analysis set with baseline and at least 1 post-baseline radiographic assessment (computed tomography (CT)/ magnetic resonance imaging (MRI) scan) for RECIST 1.1/PCWG3 related efficacy endpoints. ORR per modified RECIST 1.1/PCWG3 will be based on Response Efficacy analysis set for patients with measurable disease at baseline (see Section 10.4.13 Measurable Disease at Baseline
10.4.13 Measurable Disease at Baseline
).

10.0 Conventions and Derivations

10.1 Baseline and Change from Baseline

For the purposes of quantitative laboratory tests and assessment of changes from baseline, baseline is defined as the last available observation prior to or on the first administration of ARV-110 and on-study abiraterone. Any assessments on the same day as the first dose would be considered baseline as long as the assessment time is prior to time of the first administration of ARV-110 and on-study abiraterone. If time is not collected, the schedule of activities from Section 3 of the protocol should be used to assess if the assessment was pre or post-first administration of ARV-110 and on-study abiraterone

Change from baseline is defined as the post-baseline value minus the baseline value. Change from baseline will only be calculated for patients who have both baseline and at least one post-baseline value for parameter.

Percentage change from baseline = 100 x (Change from Baseline / Baseline Value)

10.2 Durations

- Time Since [Event] (months) = (Informed Consent Date - Event Date) / 30.4375 where the Event is either initial diagnosis, locally advanced disease, metastatic disease or most recent progression
- Duration of Exposure (weeks) = [(Last Dose Date - First Dose Date) + 1] / 7
- Duration of [Event] (months) = (Event End Date – Event Start Date + 1) / 30.4375
- Duration of abiraterone treatment = C1D1 Date - Start Date, where Start Date is the start date of abiraterone prior to study

10.3 Prior, Concomitant and Post Treatment Medications

Prior medications are defined as any medication with a start date and end date prior to the day of first dose of ARV-110 and abiraterone.

Concomitant medications are defined as any non-study medication or vaccine (including over-the-counter or prescription medicines, vitamins, physiologic replacement doses of systemically administered corticosteroids and/or herbal supplements) that the patient receives on or after the day of first dose of study medication, up to and including 30 days after the last dose of study medication.

Post-treatment medications are medications that started beyond 30 days of last dose of study medication.

10.4 Efficacy

CT, MRI scans and bone scans will be done every 8 weeks (±5 days) for the first 24 weeks of study treatment, then every 12 weeks (±5 days) thereafter, until radiographically and/or clinically 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). Modified

PCWG3 (bone) and RECIST version1.1 (soft tissue) guidelines will be used to determine each patient's visit response according to target lesions, non-target lesions, new lesions and bone lesions. The visit response categories per RECIST 1.1, include CR, PR, SD, Non-CR/Non-PD, PD, Not Evaluable (NE), No Evidence of Disease (NED), and Not Applicable (NA). The bone response categories per PCWG3 include non-PD, PD, unconfirmed progression, NE, no evidence of disease (NED), and not applicable.

Patients with no lesions per RECIST 1.1 or PCWG3 at screening will be documented as NED. Overall RECIST 1.1 soft tissue response is assigned NED when there are no target lesions and no non-target lesions at screening and no new soft tissue lesions at the applicable imaging visit. Bone Scan Response is assigned NED when there are no bone lesions on screening bone scan and there are no new bone lesions on the applicable visit bone scan. Overall Radiographic Response (combined RECIST 1.1 soft tissue and PCWG3 bone) is assigned NED when Overall RECIST 1.1 soft tissue response and Bone Response are both NED.

10.4.1 PSA Progression

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.

Time to PSA progression is the time interval from the date of first ARV-110 dose to the date of PSA progression. The patients who do not have PSA progression will be censored on the date of the last PSA assessment before receipt of new anti-cancer therapy. If the patient does not have post-baseline PSA assessment, the patients will be censored on the date of first ARV-110 dose.

Reasons for censoring will be classified as:

- Patients who are PSA progression-free at data cutoff or End of Study;
- Patients who are lost to follow-up or withdraw consent;
- Patients given subsequent anti-cancer treatment prior to PSA progression;
- Patients who are PSA progression-free prior to death on-study.

The time to PSA progression is calculated as:

Time to PSA progression (months) = (Date of PSA progression - Date of First Dose + 1) / 30.4375.

10.4.2 PSA Control

PSA control is defined as the lack of PSA progression at 12 weeks.

The PSA control rate is the proportion of patients with PSA control at 12 weeks. The number of patients in the PSA Efficacy analysis set will be used as the denominator in the analysis.

10.4.3 PSA50 Response

A PSA50 response is defined as a ≥50% decline in PSA from baseline. This PSA decline must be confirmed by a second PSA value which has a ≥50% decline from baseline obtained 3 or more weeks later.

The PSA50 response rate is the proportion of patients with a confirmed PSA50 response. The number of patients in the PSA Efficacy analysis set will be used as the denominator in the analysis. The rate of unconfirmed PSA50 response, i.e., the proportion of patients with at least one record of ≥50% decline in PSA from baseline regardless of PSA records thereafter, will also be reported separately.

10.4.4 Duration of PSA50 Response

Duration of PSA50 response is the time interval from the date of first confirmed PSA50 response to the date of PSA progression.

Any patient who does not have confirmed PSA progression will be censored on the date of their last evaluable PSA assessment, prior to any new subsequent anti-cancer therapy.

Reasons for censoring will be classified as:

- Patients on-study and progression-free at data cutoff or End of Study;
- Patients who are lost to follow-up or withdraw consent;
- Patients given subsequent anti-cancer treatment prior to PSA progression;
- Death on-study.

The duration of PSA50 response is calculated as:

- Duration of PSA50 response (months) = (Date of confirmed PSA progression - Date of First Confirmed PSA50 response + 1) / 30.4375.

10.4.5 PSA30 Response

A PSA30 response is defined as a ≥30% decline in PSA from baseline. This PSA decline must be confirmed by a second PSA value which has a ≥30% decline from baseline obtained 3 or more weeks (≥21 days) later.

The PSA30 response rate is the proportion of patients with a confirmed PSA30 response. The number of patients in the PSA Efficacy analysis set will be used as the denominator in the analysis. The rate of unconfirmed PSA30 response, i.e., the proportion of patients with at least one record of ≥30% decline in PSA from baseline regardless of PSA records thereafter, will also be reported separately.

10.4.6 Duration of PSA30 Response

Duration of PSA30 response is the time interval from the date of first confirmed PSA30 response to the date of confirmed PSA progression.

Any patient who does not have confirmed PSA progression will be censored on the date of their last evaluable PSA assessment, prior to any new subsequent anti-cancer therapy.

Reasons for censoring will be classified as:

- Patients on-study and progression-free at data cutoff or End of Study;
- Patients who are lost to follow-up or withdraw consent;
- Patients given subsequent anti-cancer treatment prior to PSA progression;
- Death on-study.

The duration of PSA30 response is calculated as:

- Duration of PSA30 response (months) = (Date of confirmed PSA progression - Date of First Confirmed PSA30 response + 1) / 30.4375.

10.4.7 Confirmation of Response by Modified RECIST 1.1/PCWG3

Confirmed responses (CR, PR), are those performed at least 4 weeks after the criteria for initial response were first met. These confirmed responses will be used in the derivations for ORR and DOR. Refer to Table 1 for the algorithm defining confirmed response.

Table 1 Confirmed Response based on Subsequent Assessments*

First Time Point Response**	Second Time Point Response	Confirmed Response (Best Response)*
PD (soft tissue)	Any Status	PD
PD (bone)	PD (bone)	PD
PD (bone)	No further evaluation	SD or NE (2)
PD (bone)	Any Status	SD or NE (2)
NE	PD	PD
CR	PD	SD or PD (1)
PR	PD	SD or PD (1)
SD	PD	SD or PD (1)
CR	CR	CR
CR	NE **	SD or NE (2)
PR	CR	PR
PR	PR	PR
PR	SD (3)**	SD
PR	NE **	SD or NE (2)
SD	CR	SD
SD	PR	SD
SD	SD	SD
SD	NE	SD or NE (2)
NE	CR	SD
NE	PR	SD
NE	SD	SD
NE	NE	NE
NED	NED or PD or uPD or NE	NED

* A Best Response of SD can only be made after the patient is on-study for a minimum of 42 days. If the patient is on-study less than 42 days, any tumor assessment indicating SD before this time period will have a Best Response of NE unless PD is identified.

** Subsequent documentation of CR may provide confirmation of a previously identified CR for patients where the second integrated response was NE. Subsequent documentation of PR may provide confirmation of a previously identified PR for patients where the second integrated response was NE or SD. If the third time point response confirms the CR (or PR) then the confirmed response will be CR (or PR). For this study, only one intervening NE is allowed between CRs/PRs. For example: CR NE CR = CR; PR NE PR = PR. Additionally, one SD is allowed between PRs (e.g., PR SD PR = PR).

1) Best response will be SD if the first time point response is after at least 42 days on-treatment. Otherwise, the best response will be PD if the PD was from soft tissue.
2) Best response will be SD if the first time point response is after 42 days on-study. Otherwise, the best response will be NE.
3) Time point response is SD if the increase from the first to the second assessment does not qualify for PD.

Unconfirmed responses (CR, PR), are those only have one record of CR/PR without subsequently second scan being confirmed by 4 weeks apart.

For patients with unconfirmed CR/PR and who subsequently discontinue study participation early, the best overall response (BOR) will be SD.

10.4.8 Confirmed Progression by Modified RECIST 1.1/PCWG3

PD within bone lesions (identified on bone scan) will be assessed only by PCWG3. For these lesions, PD must be confirmed at least 6 weeks after PD was first identified according to the criteria in Table 2 below:

Table 2 *Confirmed Progression by Modified RECIST 1.1/PCWG3*

Date Progression Detected (a)	Criteria for Progression	Criteria for Confirmed Progression	Criteria to Document Disease Progression on Confirmatory Scan
Week 8	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
Week 16 or later	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	Persistent or increase in number of bone lesions on bone scan compared to prior scan (c)

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).

10.4.9 Best Overall Response by Modified RECIST 1.1/PCWG3

The best overall response is the best response recorded from the start of the study treatment until the earliest of the following:

- Lost to follow-up or withdraw consent;
- Subsequent anti-cancer treatment;
- Death.

10.4.10 Overall Response Rate

ORR is defined as the percentage of patients with a BOR of confirmed CR or confirmed PR, where response is determined from all visit responses using the following sequential order: CR, PR, SD, PD, and NE. The number of patients in the Response Efficacy analysis set with measurable disease at baseline (see Section 0) will be used as the denominator.

ORR is based on confirmed responses per modified RECIST v1.1 / PCWG3 bone.

10.4.11 Duration of Response

DOR is defined as the time interval from the date of first documented confirmed CR/PR to the date of PD (per modified RECIST 1.1/PCWG3 criteria) or death, whichever occurs first. The number of patients in the Response Efficacy analysis set with measurable disease at baseline (see Section 0) who had a confirmed BOR of CR or PR, will be used in the analysis.

Any patient who does not have documented PD will be censored on the date of their last evaluable assessment, as per the following guidelines:

- Patients on-study and progression-free at data cutoff or End of Study;
- Patients who are lost to follow-up or withdraw consent;
- Patients given alternative cancer treatment prior to PD or death on-study;

The DOR is calculated as:

- DOR (months) = (Date of PD or Death - Date of First Documented Confirmed CR/PR + 1) / 30.4375.

10.4.12 Radiographic Progression-Free Survival

Radiographic progression-free survival (rPFS) 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 anti-cancer therapy. If the patient is alive and does not have a post-baseline imaging assessment, the patient will be censored on the date of first ARV-110 dose.

The rPFS time is calculated as:

- rPFS time (months) = (Date of PD or Death - Date of First Study Dose + 1) / 30.4375 (months).

PFS data will be censored for the patients who do not have documented PD or death. The following censoring rules that will be used:

- Event time will be censored on the date of the first dose with duration of 1 day for
    - Patients lacking any evaluation of disease after first study treatment (unless, they die within 2 tumor assessments of baseline, this will be treated as an event with the date of death as the event date).
- Event time will be censored on the date of the last evaluable assessment documenting absence of PD for:
    - Patients progression-free at data cutoff;
    - Patients who are lost to follow-up or withdraw consent;
    - Patients given alternative cancer treatment prior to PD or death.
- Event time will be censored on the date of the last evaluable assessment if PD occurs after at least two missing tumor assessments

10.4.13 Measurable Disease at Baseline

Measurable disease at baseline will be defined as patients who have at least one target lesion per modified RECIST v1.1 as assessed by the investigator at baseline.

10.5 Study Drug Exposure

10.5.1 Number of Doses Received

Equal to the number of unique dose administrations received where unique is defined as a single administration of ARV-110.

10.5.2 Cumulative Dose Received

Cumulative dose received (mg) is defined as the total amount of the study drug a patient receives during the study, that is, the sum of (Actual dose received [mg] recorded on Dosing Log eCRF page) = sum (number of days * actual dose per administration [mg] recorded on Dosing Log eCRF page).

10.5.3 Dose Intensity and Compliance

Absolute Dose Intensity is calculated as;

- Cumulative Dose Received (mg) / Duration of Exposure (weeks).

Relative Dose Intensity is calculated as;

- Cumulative Dose Received (mg) / Planned Cumulative Dose (mg)

The planned cumulative dose is calculated as the starting daily dose multiplied by the number of days between the actual date of first dose and the actual date of last dose, i.e., duration of exposure.

Compliance is calculated as;

- Cumulative Dose Received (mg) / Planned Cumulative Dose (mg), accounting for dose decreases and interruptions as per physician's decision.

Noncompliance is defined as receiving less than 80% or more than 120% of assigned study drug at any visit.

10.6 Safety Variables

10.6.1 Dose-Limiting Toxicity

DLTs will be evaluated during the first cycle and identified on the 'Dose Limiting Toxicity' eCRF page. Refer to Section 6.2 of the protocol for the definition of a DLT.

10.6.2 Safety Lead-in

Patients from the safety lead-in are defined as those indicated as "Patients in Safety Lead-In" on the eCRF page.

10.6.3 Treatment-Emergent Adverse Event

A treatment-emergent adverse event (TEAE) is an AE occurring on/after the date of first dose of ARV-110 and on-study abiraterone and within 30 days of the last dose of ARV-110 and on-study abiraterone.

10.6.4 Laboratory Parameters

Clinical laboratory parameters to be collected routinely for hematology, chemistry, coagulation, and urinalysis. Other laboratory parameters are collected for viral serology, thyroid profile, serum testosterone, and PSA. All parameters are listed in 15.3 Appendix 3.

10.6.5 Potential Hepatotoxicity and Liver Function Test

Elevated aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin and alkaline phosphatase (ALP) will be summarized as a function of the upper limit of normal (ULN):

- AST ≥ 3x ULN, ≥ 5x ULN, ≥ 10x ULN, and ≥ 20x ULN
- ALT ≥ 3x ULN, ≥ 5x ULN, ≥ 10x ULN, and ≥ 20x ULN
- (AST or ALT) ≥ 3x ULN, ≥ 5x ULN, ≥ 10x ULN, and ≥ 20x ULN
- Total Bilirubin: ≥ 2x ULN
- Concurrent ALT>=3xULN and TBILI >= 2xULN
- Concurrent AST>=3xULN and TBILI >= 2xULN
- Concurrent (ALT or AST) >=3xULN and TBILI >= 2xULN
- Concurrent (ALT or AST) >=3xULN and TBILI >= 2xULN and ALP < 2xULN
- Concurrent (ALT or AST) >=3xULN and TBILI >= 2xULN and ALP >=2xULN

'Concurrent' means the AST or ALT value preceded the TBili and ALP increase within (≤) 30 days.

An eDISH Plot of ALT/AST and Total Bilirubin will also be presented utilizing Hy's Law where potential DILI is defined as ALT or AST ≥ 3 × ULN and total bilirubin ≥ 2 × ULN reported anytime during treatment.

10.6.6 Electrocardiogram Corrected QT Intervals

The corrected QT interval by Fredericia's method (QTcF) is collected on the CRF. If duplicate/triplicates of QTcF are available at a given time point, the average will be derived. Both the average values and all of the individual measurements should be provided in the data listings.

10.7 Handling of Partial Dates

No imputation for missing or partial dates prior to enrollment will be performed (e.g. Diagnosis Date). Any durations based on these dates will therefore also be missing.

Rules for the imputation of prior and concomitant medications and adverse events are in 15.1 Appendix 1 and 15.2 Appendix 2.

10.8 Other Derived Variables

10.8.1 Age

Age in years at informed consent is collected in the 'Demographics' page in the eCRF. If age is missing, it will be calculated as follows:

(Date of informed consent signed – birth year) / 365.2425

10.8.2 Worst Post-Baseline Grade

The worst post-baseline grade will be derived by taking the highest grading, including unscheduled visits, on or after the first dose of ARV-110 and no later than 30 days after the last dose of ARV-110. For laboratory parameters in both directions (high and low, see 15.3 Appendix 3) the worst grade will be derived in both directions.

11.0 Interim Analyses

No formal interim analyses are planned for this study.

12.0 Statistical Methods

All data collected during this study will be displayed in patient data listings, unless otherwise specified. Data listings will be sorted by cohort and patient identifier.

Data will be summarized for patients in the safety lead-in and for all patients except for efficacy analysis, which will be summarized for all patients only given limited sample size.

Continuous variables will be summarized using the number of observati`ons (n), mean, Standard Deviation (STD), median, minimum and maximum. The minimum and maximum values will be displayed to the same level of precision as the raw data, the mean, median, Q1, and Q3 to a further decimal place and the SD to two additional decimal places. Pharmacokinetic summaries will additionally include number of non-BLQ (below the limit of quantitation) concentrations (concentration summaries only), CV%, geometric mean, and geometric CV% with the exception of Tmax for which only number of observations, median, minimum, and maximum will be presented.

Categorical variables will be summarized using counts and percentages. Percentages will be rounded to one decimal place, except 100% will be displayed without any decimal places and percentages will not be displayed for zero counts. Percentages will be rounded to one decimal place, except 100% will be displayed without any decimal place and percentages will not be displayed for zero counts. Time-to-event data will be presented using KM and Swimmer plots.

Unless otherwise noted, values for missing safety laboratory and vital sign values will not be imputed. However, a missing baseline result will be replaced with a screening result, if available. If safety laboratory values for a patient are missing for any reason at a time point, the patient will be excluded from the calculation of summary statistics for that time point.

If there are multiple records for an assessment time point, the records will be sorted in chronological order and the last record will be used for analyses.

For analyses of laboratory data that are continuous in nature, values at the lower/upper limit of quantification will be imputed to the value of the lower or upper limit minus or plus 1 significant digit, respectively (e.g., if the result of a continuous laboratory test is < 30, a value of 29 will be assigned; if the result of a continuous laboratory test is < 30.0, a value of 29.9 will be assigned). If the result of continuous lab test is <1, the imputed value should be 0.9; If the result of the lab test is <0.1, the imputed value should be 0.09. The actual reported values will be provided in by-patient listings.

Other approaches for dealing with missing data for prior and concomitant medication and adverse events can be found in 15.1 Appendix 1 and 15.2 Appendix 2.

12.0.1 Daylight Savings Time Adjustments

On November 5th, 2023 at 2:00 am the clocks change to 1:00 am as Daylight Savings Time ends. All clinic procedures for the remainder of the treatment period will be moved back by one hour after daylight savings time ends. All duration (ie, relative time from dosing for PK) calculations for times post-daylight savings time adjustment that will be relative to a time prior to daylight savings will need to be programmatically adjusted for the hour that was gained on the morning of November 5th.

On March 10th, 2024 at 2:00 am the clocks change to 3:00 am for Daylight Savings Time. All clinic procedures for the remainder of the treatment period will be moved forward by one hour after daylight savings time occurs. All duration calculations (ie, AE duration, relative time from dosing for PK) for times post-daylight savings time that will be relative to a time prior to daylight savings will need to be programmatically adjusted for the hour that was lost on the morning of March 10th.

Daylight saving time should be adjusted if the samples withdrawn in previous years.

12.1 Patient Disposition

The disposition of patients in the Enrolled analysis set will be summarized descriptively for: Patients within each analysis set.

Patients enrolled, screen failed, who took treatment, who are still on-treatment, who discontinued treatment/study, along with the reasons for discontinuation, and who completed the study.

A listing of screen failures will also be produced.

12.2 Demographic and Baseline Characteristics

The demographic, baseline characteristics and medical history (including prostate cancer history) will be presented for patients in the All-Treated analysis set.

The demographic and baseline variables, including race, ethnicity, age (years), height (cm), weight (kg), body mass index (BMI) (kg/m2), Eastern Cooperative Oncology Group (ECOG) performance status, AR mutation status (878/875, L702H, and any mutation within the number range of 671 to 920 excluding 878/875 or L702H), will be presented by frequency and percentage.

Prostate cancer history will be summarized for patients in the All-Treated analysis set. The number and percentage will be presented for the following:

- Historical classification at initial diagnosis
- Gleason primary score at initial diagnosis
- Gleason secondary score at initial diagnosis
- AJCC clinical tumor stage at initial diagnosis
- AJCC regional lymph nodes stage at initial diagnosis
- AJCC distant metastasis stage at initial diagnosis
- AJCC anatomic stage at initial diagnosis

Prior systemic anti-cancer therapy for abiraterone will be summarized for patients in the All-Treated analysis set. The number and percentage will be presented for the following:

- Disease status at start of abiraterone

Prior systemic anti-cancer therapy will be summarized for patients in the All-Treated analysis set. The number and percentage will be presented for the following:

- Type of therapy

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 25.0 or higher and will be presented by…

12.3 Treatments

12.3.1 Extent of Study Drug Exposure

Exposure for ARV-110 and abiraterone will be summarized separately for patients in the All-Treated analysis set. Descriptive statistics will be provided for the duration of exposure (weeks) (see Section 0), number of doses received, cumulative dose received (mg) absolute and relative dose intensities as well as compliance (see Section 0). The number and percentage of patients with compliance ≥ 80% - ≤ 120% will also be presented. Patients with at least 1 dose adjusted will also be presented. A swimmer plot for duration of exposure will also be presented.

12.3.2 Prior and Concomitant Medications

All medications received will be coded using World Health Organization Drug Dictionary (WHODD) (Version March 2022 [Global B3] or higher).

Concomitant medications will be summarized and will include the number and percentage of patients who received at least one medication and the number and percentage of patients who received at least one medication by anatomical therapeutic chemical (ATC) classification level 2 and preferred drug name.

All medications will be provided in a by-patient listing, along with a column indicating whether the medication was prior or concomitant.

A summary of prior anti-cancer therapies will be presented for all settings, including therapy setting, type of therapy, whether patients progressed on most recent regimen, time since most recent progression (see Section 0), number of prior hormonal regimens, duration of the most recent prior hormonal regimen (see Section 0) and selected prior medications of interest. Also specifically within the metastatic setting, including number of prior regimens and prior chemotherapy regimens.

Handling of missing or partial dates is defined in 15.1 Appendix 1.

12.4 Protocol Deviations

Protocol deviations data will be entered into a Clinical Trials Management System (CTMS). The study team and the sponsor will conduct on-going reviews of the deviation data from CTMS.

Deviations will be categorized as: inclusion/exclusion criteria not met, study drug deviation, prohibited medication received, overdose/misuse, study procedures not performed, out of visit window, etc. The study team will also categorize protocol deviations as important or not important. Final review of protocol deviations will be conducted and finalized prior to locking the database.

The number of patients with at least one important protocol deviation within each deviation category will be presented based on the All-Treated analysis set. Important and non-important protocol deviations are defined per the study Protocol Deviation Guidance document.

COVID-19 related protocol deviations will be defined in CTMS using a standard naming convention. These deviation descriptions will start with ‘Covid 19:’. The ICON programming team will use this standard naming convention to flag for COVID-19 deviations within the analysis datasets.

A listing of protocol deviations will be provided.

12.5 Efficacy Analyses

The Response Efficacy analysis set will be used for analysis of the RECIST v1.1 tumor assessment endpoints (ORR and DOR). The All-Treated Analysis Set will be used for the analysis of rPFS. The PSA Efficacy analysis set will be used for the analysis of PSA control rate, PSA30 response, PSA50 response, time to PSA progression, duration of PSA30 response, and duration of PSA50 response.

12.5.1 Hypothesis Testing Strategy and Multiplicity

No planned formal hypothesis testing.

12.5.2 Primary Analysis

There are no primary efficacy endpoints defined for this study.

12.5.3 Secondary Analysis

12.5.3.1 PSA Control Rate

The number of patients in the PSA Efficacy analysis set will be used as the denominator for PSA control rate (see Section 0). The count and percentage of patients with PSA control will be presented along with two-sided 95% CI for the percentage, estimated using the Clopper-Pearson exact method (Clopper CJ & Pearson ES, 1934).

In addition, PSA will also be presented at each cycle day 1 visit for absolute, change from baseline, and percent change from baseline. PSA data will be presented using a spider plot.

12.5.3.2 PSA50 Response Rate

The number of patients in the PSA Efficacy analysis set will be used as the denominator for PSA50 response rate (see Section 0). The count and percentage of patients with PSA50 response will be presented along with two-sided 95% CI for the percentage, estimated using the Clopper-Pearson exact method (Clopper CJ & Pearson ES, 1934).

12.5.3.3 Duration of PSA50 Response

Providing there are at least 5 PSA50 responses overall, the duration of PSA50 response will be estimated using Kaplan-Meier (KM) product-limit method for patients in the PSA Efficacy analysis set with a PSA50 response.

The median duration of PSA50 response and its two sided 95% CIs (Brookmeyer and Crowley, 1982) will be calculated where appropriate. The count and percent of responding patients who have an event or are censored will be summarized. Refer to Section 10.4.4 or censoring rules.

In the case that there are less than 5 responders overall, duration of PSA50 will be listed only.

12.5.3.4 PSA30 Response Rate

PSA30 response rate (see Section 0) will be analyzed in the same way as PSA50 response rate.

12.5.3.5 Duration of PSA30 Response

Duration of PSA30 response (see Section 0) will be analyzed in the same way as duration of PSA50 response.

12.5.3.6 Time to PSA Progression

If PSA progression is reported for at least 5 patients, time to PSA progression (see Section 0) will be estimated using Kaplan-Meier (KM) product-limit for patients in the PSA Efficacy analysis set. The number and percentage of patients with an event (PSA progression) or are censored will be presented.

The median of time to PSA progression and its two sided 95% CIs (Brookmeyer and Crowley, 1982) will be calculated where appropriate.

Time to PSA progression will be presented graphically in the form of both a KM plot and swimmer plot. In the case that there are less than 5 patients with PSA progressions, the PSA progressions will be listed only.

12.5.3.7 Radiographic Progression-Free Survival

The All-Treated analysis set will be used for analysis of rPFS. The number and percentage of patients with an event (PD or death) will be presented.KM estimates together with the median of survival time and its two-sided 95% CIs (Brookmeyer and Crowley, 1982) will be presented in a KM plot.

12.5.3.8 Overall Response Rate

The number of patients in the Response Efficacy analysis set with measurable disease at baseline (see Section 0) will be used as the denominator for ORR. The count and percentage of patients with an overall response will be presented along with two-sided 95% CI for the percentage, estimated using the Clopper-Pearson exact method. Counts and percentages of patients with a BOR of confirmed CR, confirmed PR, SD, PD or NE will also be presented.

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.

Spider plots will also be provided at the patient level, displaying the duration of treatment overlaid with the BOR.

12.5.3.9 Duration of Response

Providing there are at least 5 responders overall, DOR (see Section 0) will be summarized descriptively using the KM estimate, based on patients in the Response Efficacy analysis set with measurable disease at baseline who had a BOR of confirmed CR or confirmed PR.

The median of DOR and its two sided 95% CIs (Brookmeyer and Crowley, 1982) will be calculated where appropriate. The count and percent of responding patients who have an event or are censored will be summarized.

DOR will also be presented graphically in the form of both a KM plot and a swimmer plot.

If there are less than 5 responders overall, DOR will be listed only.

12.6 Safety Analyses

Safety analyses will be performed within the All-Treated Analysis Set.

12.6.1 Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) (version 20.1 or higher) and will be graded using NCI CTCAE version 5.0.

Handling of missing or partial dates is defined in 15.2 Appendix 2.

An overall summary of TEAEs will be provided and will include summaries of patients with the following:

- DLTs during first treatment cycle for safety lead-in
- Any TEAE,
- Any TEAE by maximum CTCAE toxicity grade (Grade 1 – Grade 5)
- Any grade 3 or greater TEAE
- Any (ARV-110)-related TEAE
- Any (abiraterone)-related TEAE
- Any ARV-110 or abiraterone related TEAE
- Any grade 3 or higher (ARV-110)-related TEAE
- Any grade 3 or higher (abiraterone)-related TEAE
- Any grade 3 or higher, ARV-110 or abiraterone related TEAE
- Any TEAE with outcome of death
- Any serious TEAE
- Any serious (ARV-110)-related TEAE
- Any serious (abiraterone)-related TEAE
- Any serious, ARV-110 or abiraterone related TEAE
- Any TEAE leading to reduction of ARV-110

- Any TEAE leading to reduction of abiraterone
- Any TEAE leading to interruption of abiraterone
- Any TEAE leading to interruption of ARV-110
- Any TEAE leading to discontinuation of ARV-110
- Any TEAE leading to discontinuation of abiraterone
- Any (ARV-110)-related TEAE leading to discontinuation of ARV-110
- Any (abiraterone)-related TEAE leading to discontinuation of abiraterone

The total number of TEAEs in each of the above listed categories will also be presented.

Summaries (number and percentage of patients and number of events) of TEAEs by system organ class (SOC) and preferred term (PT) will be provided. Note that counting will be by patient, not event, and patients are only counted once, with worst CTCAE grade if multiple same events reported, within each SOC and PT.

Summaries will include the following:

- CTCAE Grade 3 or higher TEAEs by SOC and PT

Further, the number and percentage of patients with the following types of TEAEs will be summarized by SOC, PT and maximum CTCAE grade:

- First Cycle DLTs for safety lead-in
- TEAEs
- Treatment (ARV-110)-related TEAEs
- Treatment (abiraterone)-related TEAEs
- TEAEs leading to discontinuation of ARV-110
- TEAEs leading to discontinuation of abiraterone
- Treatment (ARV-110)-related TEAEs leading to discontinuation of ARV-110
- Treatment (abiraterone)-related TEAEs leading to discontinuation of abiraterone
- Treatment (ARV-110)-related TEAEs leading to discontinuation of ARV-110 and abiraterone
- TEAEs leading to an interruption of ARV-110
- TEAEs leading to an interruption of abiraterone
- Treatment (ARV-110)-related TEAEs leading to an interruption of ARV-110
- Treatment (abiraterone)-related TEAEs leading to an interruption of abiraterone
- Treatment (ARV-110)-related TEAEs leading to an interruption of ARV-110 and abiraterone
- TEAEs leading to a dose reduction of ARV-110
- TEAEs leading to a dose reduction of abiraterone
- Treatment (ARV-110)-related TEAEs leading to a dose reduction of ARV-110
- Treatment (abiraterone)-related TEAEs leading to a dose reduction of abiraterone

All adverse events (including non-treatment-emergent events) will be provided in a by-patient listing. In addition, by-patient listings will be provided for CTCAE Grade 3 or higher TEAES and TEAEs leading to study discontinuation.

12.6.2 Deaths and Serious Adverse Events

The following summaries will be presented:

- Table listing of TEAEs with Outcome of Death
- Table listing of Serious TEAEs
- Serious TEAEs by SOC, PT and Maximum CTCAE Grade
- Serious Treatment (ARV-110)-Related TEAEs by SOC and PT
- Serious Treatment (Abiraterone)-Related TEAEs by SOC and PT
- Treatment (ARV-110)-Related Serious TEAEs by SOC, PT and Maximum CTCAE Grade
- Treatment (Abiraterone)-Related Serious TEAEs by SOC, PT and Maximum CTCAE Grade

An additional summary presenting all deaths, along with details displaying the primary cause of death and the number of deaths within/after 30 days of the last study medication, related to disease under study or complications, and other will also be presented.

12.6.3 Laboratory Data

Clinical laboratory parameters to be collected routinely for hematology, chemistry, coagulation and urinalysis. Other laboratory parameters are collected for viral serology, thyroid function, serum testosterone and PSA assessments.

Laboratory data will be analyzed in System International (SI) units.

NCI CTCAE v5.0 grades will be applied for selected hematology and chemistry parameters, indicated in 15.3 Appendix 3 by the notation of Low, High, High or Low.

Grades are applied based only on the numeric SI value of the parameter assessed; clinical signs and symptoms are not considered.

Unscheduled laboratory measurements will be included in the analysis of the worst grade for NCI-CTCAE gradable parameters.

12.6.3.1 Hematology and Clinical Chemistry

Selected parameters will be graded by NCI-CTCAE version 5.0, refer to 15.3 Appendix 3 for the full list of protocol required parameters, including those selected for CTCAE grading.

Descriptive summaries of the baseline toxicity grade and worst post-baseline toxicity grade will be summarized, in addition, shifts from baseline to worst post-baseline will also be presented.

In order to assess potential hepatotoxicity, the number and percentage of patients with elevated AST, ALT, total bilirubin and ALP will be summarized as a function of the ULN, defined in 10.6.4.

Hematology and clinical chemistry parameters will be listed separately, with associated NCI-CTCAE grades and normal ranges also displayed.

12.6.3.2 Vital Signs

Values for weight, systolic and diastolic blood pressure (mmHg), heart rate (beats/min), respiratory rate (breaths/min), temperature (°C), with abnormal findings will be listed

12.6.3.3 Other Laboratory Parameters

Other laboratory data, with categories including thyroid function will be listed only.

12.6.4 Physical Examinations, ECGs, and Other Observations Related to Safety

12.6.4.1 Physical Examinations

Abnormal physical examination results will be provided in by-patient listings.

12.6.4.2 Electrocardiogram

Single 12-lead standard electrocardiogram (ECG) will be obtained using an ECG machine that automatically calculates the heart rate (beats/min) and measures PR interval (msec), QRS duration (msec), QT interval (msec), and QTcF intervals (msec).

RR interval values will be derived using the following:

- RR interval (milliseconds) = 60,000 / HR (bpm)

The following will be summarized for ECG results:

- Change of ECG parameters from baseline by visit and overall interpretation results (including mean, median, standard deviation, maximum, and minimum)
- The number and percentage of patients with maximum post-baseline on-treatment QTcF values <450, ≥450 to <480, ≥480 to <500, ≥500 msec
- The number and percentage of patients with the QTcF maximum change from baseline as <30, ≥30 to <60, ≥60 msec
- Overall shift summary of QTc absolute values from baseline to worst post-baseline with values <450, ≥450 to <480, ≥480 to <500, ≥500 msec

Overall interpretation of ECG will be presented by result category (Normal, Abnormal, Unevaluable and Unknown) at each scheduled visit.

ECG results will also be provided in by-patient listings.

ECG results will also be listed if clinically significant with categories “Yes” and “No”.

12.6.4.3 Eastern Cooperative Oncology Group (ECOG) Performance Status

Baseline ECOG performance status will be summarized as part of the baseline characteristics, all ECOG data will be listed.

12.7 Pharmacokinetic Analyses

Plasma Concentrations

Plasma concentrations of Abiraterone and ARV-110 will be summarized by treatment and nominal time point using descriptive statistics [n, number of non-BLQ, mean, CV%, standard deviation, geometric mean, geometric CV %, min, median, and max]; Patients in the safety lead-in will be listed, summarized and plotted separately from all other patients. Plasma concentrations below the quantifiable limit (BLQ) will be set to 0 in the computation of mean concentration values.

Figures for patients in the safety lead-in with intensive PK will include:

Arithmetic mean plasma concentration-time profiles of Abiraterone (Day -1 and Cycle 1 Day 21) and ARV-110 (Cycle 1 Day 21) by scheduled sampling time will be plotted on linear (+/-STD) and semilogarithmic (+/-STD) scales.

Geometric mean concentration-time profiles of Abiraterone (Day -1 and Cycle 1 Day 21) and ARV-110 (Cycle 1 Day 21) by scheduled sampling time will be presented on linear and semilogarithmic scales. Arithmetic mean and geometric mean plots will be plotted by treatment group overlaid in the same graph (where applicable). These plots will show time in hours.

Individual Abiraterone (Day -1 and Cycle 1 Day 21) and ARV-110 (Cycle 1 Day 21) concentration-time plots by actual sampling time will be provided by patient (one patient per page) with patient concentration-time profiles overlaid by respective treatment (where applicable). These plots will show time in hours. All values reported as BLQ before the first quantifiable concentration will be set to zero and after the first quantifiable concentration will be set to missing in these plots. These plots will be provided on linear and semilogarithmic scales.

Figures for pre-dose (trough) PK:

Arithmetic mean pre-dose (trough) plasma concentration-time plots of Abiraterone and ARV-110 by study day will be plotted on linear (+/-STD) and semilogarithmic (+/-STD) scales.

Geometric mean pre-dose (trough) concentration-time plot of Abiraterone and ARV-110 by study day will be presented on linear and semilogarithmic scales. Arithmetic mean and geometric mean plots will be plotted by treatment group overlaid in the same graph (where applicable).

Individual Abiraterone and ARV-110 pre-dose (trough) concentration-time plots by study day will be provided by patient (one patient per page) with patient concentration-time profiles overlaid by respective treatment (where applicable), and plots will be provided on linear and semilogarithmic scales.

Concentrations that are BLQ will be treated as outlined in Section 12.7.1.1 for the computation of concentration summaries and derivation of individual patient PK parameters. All plasma concentrations will be presented in a data listing.

Blood samples will be collected to determine the concentrations of Abiraterone and ARV-110 in plasma at the time points listed in the protocol (see SOA).

Note, "total ARV-110" is the same as "ARV-110," and the terms may be used interchangeably for PK reporting.

12.7.1 General Considerations

12.7.1.1 Dealing with Concentrations Below the Lower Limit of Quantification

Plasma concentrations below the quantifiable limit (BLQ) will be set to 0 in the computation of mean concentration values. In estimating the PK parameters, BLQ values before the first quantifiable concentration will be set to zero and BLQ values after the first quantifiable concentration will be set to missing.

Individual BLQ results occurring between two quantifiable concentrations will be set to missing. Results reported as NRR (No Recorded Result) will be set to missing.

In log-linear plots these values would not be represented. In the tables presenting summary statistics of concentration-time series, the total number of values (n) and the number of values that are above the lower limit of quantification (LLOQ) should be presented to allow appropriate interpretation of the data.

If the majority of concentrations are BLOQ, the pharmacokineticist may choose to not report any parameters for the data in question. Alternatively, if most patients have at least one quantifiable result, it may be informative to report and summarize some limited PK parameters:

- If all concentrations in a profile are BLOQ, Cmax and AUClast may be reported as missing (Tmax is missing).
- Cmax and Tmax may be reported based on only a single quantifiable concentration if all other samples in a profile are BLOQ.
- A minimum of 3 quantifiable concentrations is recommended to report AUClast (except AUClast may be reported as missing when all concentrations are missing as noted above).
- AUCs that represent a specified time interval, such as AUCtau, should generally only be reported at the discretion of pharmacokineticist if:
    - Concentrations after Cmax remain quantifiable to the end of the interval (Tlast is ≥ tau)

12.7.1.2 Missing Values

If an entire concentration-time profile is BQL then the profile will be excluded from PK analysis. Profiles with 3 or fewer quantifiable concentrations will be flagged for exclusion.

If all concentrations at a given time point are BLQ or if the number of non-BLQ concentrations at a given time point is <3, only number of observations, number of non-BLQ concentrations, minimum, and maximum will be presented and the rest of the summary statistics will be reported as not calculable (NC). This recommendation applies to both concentration-time data summarized by nominal time, and to PK parameters summarized within an initial dose group.

12.7.1.3 Time Deviations

For plasma concentration, time deviations will be listed with a flag for all deviations that are considered to be “significant” after confirmation from sponsor and ICON pharmacokineticist ”.

- Time Deviation (%) = ((Actual Time - Planned Time) / Planned Time) *100

If Time Deviation more than 20%, we will be excluded that timepoint only from concentration summary statistics.

12.7.2 Plasma Pharmacokinetic Parameters

PK parameters (for Patients in Safety Lead-In) including but not limited to those indicated in Table 3: Plasma Pharmacokinetic Parameters

will be estimated by using non-compartmental methods with WinNonlin® (Version 8.1 or higher). The AUCs will be calculated using linear up log down method for both ARV-110 and Abiraterone. In estimating the PK parameters, BLQ values before the first quantifiable concentration will be set to zero and BLQ values after the first quantifiable concentration will be set to missing.

Actual PK sampling times will be used in the derivation of PK parameters. Actual time for nominal pre-dose samples will be set to zero for PK parameter calculations and individual concentration-time plots, unless the actual time occurs after the dose. Nominal PK sampling times may be used if the actual PK times are not recorded. If the actual time is missing, the scheduled time will be substituted and flagged.

PK parameters will be summarized by treatment as well as displayed with n (number of patients), mean, standard deviation, geometric mean, CV %, geometric CV%, median, min, and max . For Tmax and Tlast, only median, min and max will be presented. For pairwise comparison of plasma Abiraterone PK paramerers, scatterplots with individual and geometric mean values for AUClast, AUCtau and Cmax will be presented by treatment along with a connect line for each patient (ladder plots). Treatment will be on the X-axis and parameter on Y-axis.

If a PK parameter cannot be derived from a patient’s concentration data, the parameter will be coded as NC (not calculated). Note that NC values will not be generated beyond the day that a patient discontinues from the study.

For ARV-110, plasma concentrations 24 hour post dose on Cycle 1 Day 21 will be assumed to be the same as pre-dose plasma concentrations on Cycle 1 Day 21 for the purpose of calculating AUCtau parameters. For abiraterone, plasma concentrations will be extrapolated to calculate AUCtau parameters by Phoenix WNL. Tlast and AUClast will be calculated without the above modifications.

All parameters will be listed by patient, within dose group and day.

If calculable, the following PK parameters listed in Table 3 will be determined for abiraterone and ARV-110.

Table 3: Plasma Pharmacokinetic Parameters

Pharmacokinetic Parameter	**Description**	SAS Programming Notes	Summary Statistic Reporting Precision
C_{max}	Maximum observed plasma concentration, occurring at time Tmax	Cmax from WNL	5 sd[a].

T_{max}	Time of observed maximum concentration	Tmax from WNL	2 dp[a].
C_{min}	Minimum plasma concentration, obtained directly from the observed concentration versus time data	Calculated in SAS	5 sd.
AUC_{last}	Area under the plasma concentration-time curve from the time of dosing to the time of the last measurable (positive) concentration (Tlast)	AUClast from WNL	5 sd.
AUC_{tau}	Area under the plasma concentration-time curve from time zero during a dosing interval	AUCtau from WNL	5 sd.
Cmax ratio for Abiraterone	Cmax D21 of Abiraterone/Cmax D1 of Abiraterone	Calculated in SAS	5 sd.
AUClast ratio for Abiraterone	AUClast D21 of Abiraterone/AUClast D1 of Abiraterone	Calculated in SAS	5 sd.
AUCtau ratio for Abiraterone	AUCtau D21 of Abiraterone/AUCtau D1 of Abiraterone	Calculated in SAS	5 sd.
T_{last}	Time of last measurable observed concentration	Calculated in WNL	2 dp.
C_{last}	Observed concentration corresponding to Tlast	Calculated in WNL	5 sd.

[a] dp.=Decimal Places; sd.=Significant Digits.

Additional PK parameters may be calculated, as appropriate.

AUClast will be the same as AUC0-8 and AUCtau will be the same as AUC0-24.

12.7.3 Statistical Analysis of Pharmacokinetic Parameters

A comparison of the natural-log (ln)-transformed PK parameters Cmax, AUClast and AUCTAU, of abiraterone will be made to evaluate the relative bioavailability of abiraterone + ARV-110(test) versus abiraterone alone with data captured before study drugs are administered (reference), by performing a mixed linear model using SAS® PROC MIXED. The mixed linear model will include treatment as fixed effects and patients as a random effect. The inferential results (least-squares means [LSMs], difference between LSMs, and 90% CIs of the difference) will be exponentiated to the original scale. Geometric LSMs, % geometric mean ratios (GMRs), and 90% CIs will be presented.

Analysis of mixed linear model will be performed using SAS® code similar to the example code below:

PROC MIXED;
CLASS TRTA SUBJID;

MODEL AVAL = TRTA / DDFM=KR;
RANDOM SUBJID;
ESTIMATE "abiraterone + ARV-110 vs. abiraterone alone" TRTA -1 1/ cl alpha=0.1 e;
LSMEANS TRTA/ cl alpha=0.05;
RUN;

Where TRTA is A (reference, i.e., abiraterone alone before study drugs are administered), and B (test, i.e., abiraterone + ARV-110 administered on study)
Appropriate coefficients will be used based on the naming or ordering of the treatments.
Geometric LSMs will be presented in one more precision level than the associated PK parameter. GMRs and 90% CIs will be presented with 2 decimal places and intra patients CV% will be presented to 2 decimal places.

Intra patients CV% will be calculated using the formula below:

- *Intra patients = 100 × Sqrt(exp[MSE] -1),*

where MSE is mean square error and is obtained from the aforementioned mixed-effect model.

Individual Plasma abiraterone PK exposure parameters AUClast, AUCTAU, and Cmax will be presented following the statistical analysis showing the adjusted geometric mean ratio (GMR) (%) with 90% confidence intervals (CIs) for the test (Treatment B) / reference (Treatment A) comparisons along with individual ratios.

A forest plot will be presented for this statistical analysis showing the % GMR with 90% CI for the test/reference comparison for each PK exposure parameter.

12.8.1 [redacted]

[redacted]

13.0 References

International Council for Harmonisation. (1995, November 30). *Structure and Content of Clinical Study Reports*. Retrieved from https://database.ich.org/sites/default/files/E3_Guideline.pdf

International Council for Harmonisation. (1998, September). *E 9 Statistical Principles for Clinical Trials*. Retrieved from https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-9-statistical-principles-clinical-trials-step-5_en.pdf

14.0 Glossary of Abbreviations

Glossary of Abbreviations:	
ADT	Androgen Deprivation Therapy
AE	Adverse event
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
ATC	Anatomic Therapeutic Classification
AUC	Area under the plasma concentration-time curve
AUClast	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
AUCtau	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 overall response
BP	Blood pressure
BUN	Blood urea nitrogen
C	Cycle
CBC	Complete blood count
CFR	Code of Federal Regulations
CI	Confidence interval
Cmax	Maximum plasma concentration, obtained directly from the observed concentration versus time data
Clast	Observed concentration corresponding to Tlast
Cmin	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
CTCAE	Common Toxicity Criteria for Adverse Events
[redacted]	
CSR	Clinical Study Report
D	Day
DDI	Drug-drug interaction(s)
DILI	Drug-induced liver injury
DLT	Dose-limiting toxicity
DMC	Data Monitoring Committee
DOR	Duration of response
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ECHOs	Echocardiograms
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EOT	End of treatment
FAS	Full Analysis Set
HE	Health Economics
ITT	Intention-to-treat
IVRS	Interactive Voice Response System
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
mPC	Metastatic prostate cancer
MRI	Magnetic resonance imaging
NA	Not Applicable
NE	Not evaluable
NED	No Evidence of Disease
NCI	National Cancer Institute
Non-CR Non-PD	Non complete response/non progressive disease
ORR	Overall response rate

PCWG3	Prostate Cancer Working Group 3
PD	Pharmacodynamic
PD	Progressive disease
PK	Pharmacokinetic
PP	Per Protocol
PR	Partial response
PSAs	Prostate-specific antigens
PT	Prothrombin time
PT	Preferred term
QoL	Quality of Life
rPFS	Radiographic progression-free survival
RP2D	Recommended Phase 2 dose
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SD	Stable disease
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SI	System International
SOC	System organ class
STD	Standard Deviation
TEAEs	Treatment-Emergent Adverse Events
Tlast	Time of last measurable (positive) observed concentration
Tmax	Time of maximum observed concentration
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal

15.0 Appendix

15.1 Appendix 1 Prior and Concomitant Medications Start/Stop Date Imputation

In order to assign medications as either prior and/or concomitant the following rules will be used.

Parameter Direction	Missing	Conditions	Imputation
Medications Start date	Date missing Only	If the month and year of the incomplete date are the same as the month and year of the first dose date	Date of first dose date
		If Month and/or Year is not the same as the first study dose	The First day of the month
Medications End date	Date missing Only	If the month and year of the incomplete date are the same as the month and year of the last visit date	Date of the last visit date
		If Month and/or Year is not the same as the last visit date	The last day of the month, Or the end of study/death date, whichever is earliest

15.2 Appendix 2 Adverse Events Start/Stop Date Imputation

In order to assign an AE with partial dates as treatment-emergent the following rules will be used.

Parameter Direction	Missing	Conditions	Imputation
AE Start date	Date missing Only	If the month and year of the incomplete date are the same as the month and year of the first dose date	Date of first dose date
		If either the year is before the year of the first dose date or if both years are the same but the month is before the month of the first dose date	The Last day of the month
		If either the year is after the year of the first dose date or if both years are the same but the month is after the month of the first dose date	The First day of the month
AE End Date	Date missing Only	If the month and year of the incomplete date are the same as the month and year of the last visit date	The Date of the last visit date, or the last known alive date for missing death date
		If Month and/or Year is not the same as the last visit date	The last day of the month, Or the end of study/death date, whichever is earliest; Or the last known alive date for missing death date

15.3 Appendix 3 Laboratory Parameters

Table 3 - Hematology Parameters and Grading

Parameter (SI unit) – Grade Direction	CTCAE High Term	CTCAE Low Term
Platelet Count (x10E9/L) - Low		Platelet count decreased
Red Blood Cell Count (x10E12/L) - N/A		
Hemoglobin (g/L) – High	Hemoglobin increased	
Hemoglobin (g/L) - Low		Anemia
Hematocrit (L/L) - Low		
White Blood Cells (x10E9/L) - High and Low	Leukocytosis	White blood cell (WBC) decreased
White Blood Cell count with Differential		
Absolute Neutrophils (x10E9/L) - Low		Absolute neutrophils count decreased
Absolute Lymphocytes) (x10E9/L) - High and Low	Absolute lymphocytes count increased	Absolute lymphocytes count decreased
Absolute Monocytes (x10E9/L) - N/A		
Absolute Eosinophils (x10E9/L) - High	Eosinophilia	
Absolute Basophils (x10E9/L) - N/A		

Table 4 - Clinical Chemistry Parameters and Grading

Parameter (SI unit) – Grade Direction	CTCAE High Term	CTCAE Low Term
Blood urea nitrogen (BUN) or urea (mmol/L) - N/A		
Creatinine (µmol/L) - High	Creatinine increased	
Glucose (non-fasting)		
Magnesium (mmol/L) - High and Low	Hypermagnesemia	Hypomagnesemia
Potassium (mmol/L) - High and Low	Hypokalemia	Hyperkalemia
Sodium (mmol/L) - High and Low	Hypernatremia	Hyponatremia
Total calcium (mmol/L) - High and Low	Hypercalcemia	Hypocalcemia
Lactate dehydrogenase (IU/L) - High	Blood lactate dehydrogenase increased	
Albumin (g/L) - Low		Hypoalbuminemia
Uric acid (µmol/L) - N/A		
C-reactive protein (nmol/L) - N/A		
(AST/ serum glutamic-oxaloacetic transaminase (SGOT) (IU/L) - High	Aspartate transaminase (AST) increased	
ALT/ serum glutamic-pyruvic transaminase (SGPT) (IU/L) - High	Alanine transaminase (ALT) increased	
ALP (IU/L) - High	Alkaline phosphatase (ALP) increased	
Creatine kinase (µkat/L) - High	CPK increased	

Creatine kinase MB (performed if clinically indicated) (µkat/L) - N/A Chloride (mmol/L) - N/A Amylase (µkat/L) - N/A Total bilirubin (µmol/L) - High Direct, conjugated, and unconjugated bilirubin will be performed if clinically indicated (µmol/L) - N/A Total protein (g/L) - N/A Phosphorus or phosphate (mmol/L) - N/A Carbon dioxide (bicarbonate) (mmol/L) - Low	Blood bilirubin increased	Blood bicarbonate decreased

Table 5 - Coagulation Parameters and Grading

Parameter (SI unit) – Grade Direction	CTCAE High Term	CTCAE Low Term
International normalized ratio (INR) - N/A Prothrombin time (PT) (s) - N/A Partial prothrombin time (s) - N/A Activated partial thromboplastin time (APTT) (s) - High	Activated partial thromboplastin time prolonged	

Table 6 - Urinalysis Parameters

Parameters
Leucocyte esterase

Protein
Urine bilirubin
Urobilinogen
Ketones
Microscopy (if clinically indicated)
pH
Nitrites
Specific gravity
Glucose (qual)
Blood (qual)

Table 7 - Other Parameters

Category	Parameters
Viral Serology	HIV I and II Hepatitis B Virus Hepatitis C Virus
Thyroid Profile	Thyroid-stimulating hormone (TSH)
Other Tests	Prostate-specific antigen (PSA) Serum testosterone

15.4 Appendix 4 Sample Size Calculation

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.