Protocol Title	An Open-Label, Phase 1/1b Study of ORIC-944 as a Single Agent or in Combination with an Androgen Receptor Pathway Inhibitor in Patients with Metastatic Prostate Cancer
Protocol Number	ORIC-944-01
Version (Date)	5.1 (07 March 2025) – United States only
Compound	ORIC-944
Study Phase	Phase 1
Short Title	Ph 1 Study of ORIC-944 in Patients with Metastatic Prostate Cancer
Sponsor Name and Address	ORIC Pharmaceuticals, Inc. 240 East Grand Ave, 2nd Floor South San Francisco, CA 94080 USA
Regulatory Agency Identifier Numbers	IND: 156989 Australia CTN: CT-2024-CTN-03965-2 EUCT No.: 2024-515527-11

Parts I, II, & III: To evaluate the association between potential predictive biomarkers and antitumor activity of ORIC-944 as a single agent or in combination with an ARPI	Parts I, II, & III: Correlation of PRC2 protein by IHC, gene expression, somatic alterations, DNA methylation status, and disease-related molecular markers in tissue and blood collected prior to start of study treatment with antitumor activity of ORIC-944 as a single agent or in combination with an ARPI

PATIENT ELIGIBILITY:

Inclusion Criteria:

1. Aged ≥18 years at the time of signing the informed consent
2. Patients with metastatic prostate cancer
3. Must have undergone bilateral orchiectomy or be willing to continue GnRH analogue or antagonist to maintain castrate levels of testosterone throughout the duration of the study
4. Prior Therapies:
   a. Part I (single agent dose escalation): Any number of prior therapies are allowed, but must have progressed on or after at least one line of next generation ARPI (abiraterone, apalutamide, darolutamide, or enzalutamide) and must not have received more than 2 chemotherapy regimens in the mCRPC setting
   b. Part II (ARPI combination dose escalation): Must have received only 1 prior line of ARPI (abiraterone, apalutamide, darolutamide, or enzalutamide) in any setting; may have also received up to 1 prior line of chemotherapy in the mHSPC setting.
   c. Part III (ARPI combination dose optimization): In addition to up to 1 prior line of chemotherapy in the mHSPC setting:
      - Cohorts A and B: received only one 1 prior line of abiraterone in any setting
      - Cohorts C and D: received only one 1 prior line of apalutamide, darolutamide, or enzalutamide in any setting
   d. Food effect sub-studies: Must have received only 1 prior line of ARPI (abiraterone, apalutamide, darolutamide, or enzalutamide) in any setting; may have also received up to 1 prior line of chemotherapy in the mHSPC setting
5. Evidence of progressive disease by PCWG3 criteria for study entry
   a. rising PSA, defined as a minimum of 2 rising values obtained a minimum of one week apart with the latest result being at least 2.0 ng/mL (or 1.0 ng/mL if PSA rise is the only indication of progression), or
   b. confirmation of 2 new bone lesions on last systemic therapy, or
   c. soft tissue progression per RECIST 1.1
6. Measurable and/or evaluable disease ie, presence of bone lesions on a bone scan and/or at least one measurable lesion per RECIST 1.1
7. Agreement and ability to undergo on-study punch skin biopsies, as follows:

a. one pretreatment biopsy prior to enrollment on this study and

b. one post treatment biopsy after 3-4 weeks on study treatment or at End of Treatment (EOT) whichever occurs first

8. Part I only: Dose level 3 (400 mg) and higher: agreement to undergo on-study core tumor biopsies, as follows, through a procedure that is deemed to be clinically feasible and not carry significant risk:

   a. one pretreatment tumor biopsy prior to enrollment on this study and

   b. one post treatment tumor biopsy after 6-10 weeks on study treatment

   c. one EOT tumor biopsy (optional)

9. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

10. Adequate organ function as defined by the following criteria:

    a. ANC $\geq$1500 cells/mm^3 (1.5 $\times$ 10^3 cells/mm^3)

    b. Platelets $\geq$100,000 /µL (100 $\times$ 10^9 /L)

    c. Hemoglobin $\geq$9.0 g/dL (90 g/L)

    d. AST (SGOT) or ALT (SGPT) $\leq$2.5 $\times$ ULN, $\leq$5.0 $\times$ ULN for patients with liver metastases

    e. Bilirubin $\leq$1.5 $\times$ ULN; patients with a known history of Gilbert's syndrome and/or isolated elevations of indirect bilirubin are eligible

    f. Estimated glomerular filtration rate $\geq$60 mL/min

    g. QTcF $\leq$470 msec

11. Able to swallow oral medication without chewing or crushing

12. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol

Exclusion Criteria:

1. Parts II and III only: Patients with pure small-cell carcinoma (SCC) of prostate
2. Current participation in another clinical study of an investigational agent, vaccine, or device; concomitant participation in observational studies is acceptable after sponsor approval
3. Diagnosis of another malignancy within 2 years before first dose of study treatment, except for superficial skin cancers, or localized, low-grade tumors deemed cured per investigator judgement and/or not requiring active treatment with systemic therapy
4. History or presence of CNS metastases, unless previously treated and stable
5. History of seizures or any condition or medication that may predispose to seizures
6. Any other anticancer therapy within 21 days or 5 half-lives (whichever is shorter) prior to the first dose of study drug
7. Radiotherapy within 2 weeks prior to first dose of study drug (palliative radiation or stereotactic radiosurgery within 7 days prior to first dose of study drug); patients must have recovered from all radiotherapy-related toxicities

8. Major surgery within 21 days prior to first dose of study drug or incomplete recovery from adverse effects resulting from such procedure
9. History of class III or IV congestive heart failure or severe non-ischemic cardiomyopathy, unstable or poorly controlled angina, myocardial infarction, or ventricular arrhythmia within the previous 6 months of first dose of study drug
10. Known human immunodeficiency virus (HIV) infection, unless patient is healthy and has a low risk of AIDS-related outcomes
11. Active symptomatic Hepatitis B or C infection; patients with well controlled disease are eligible
12. Active gastrointestinal disease (eg, Crohn's disease, ulcerative colitis, short gut syndrome, etc) or other malabsorption syndromes that would reasonably impact drug absorption per investigator judgement
13. Any other condition or circumstance (eg, clinical, psychological, familial, sociological, inability to swallow oral study drug) that, in the opinion of the investigator, may interfere with protocol compliance or contraindicates participation in the study

Dose and Route of Administration: ORIC-944 will be dosed orally once daily in 28-day cycles. ARPI dosing will be as per the respective prescribing information.

Safety Review Committee (SRC): A SRC consisting of study investigators and sponsor representatives will be instituted to monitor study progress and patient safety on an ongoing basis throughout the study (Section 10).