# Trial of RucaparIb in ProsTate IndicatiONs 2 (TRITON2): A Multicenter, Open-Label Phase 2 Study of the PARP Inhibitor Rucaparib in Patients with Metastatic Castration-Resistant Prostate Cancer Associated with Homologous Recombination Deficiency

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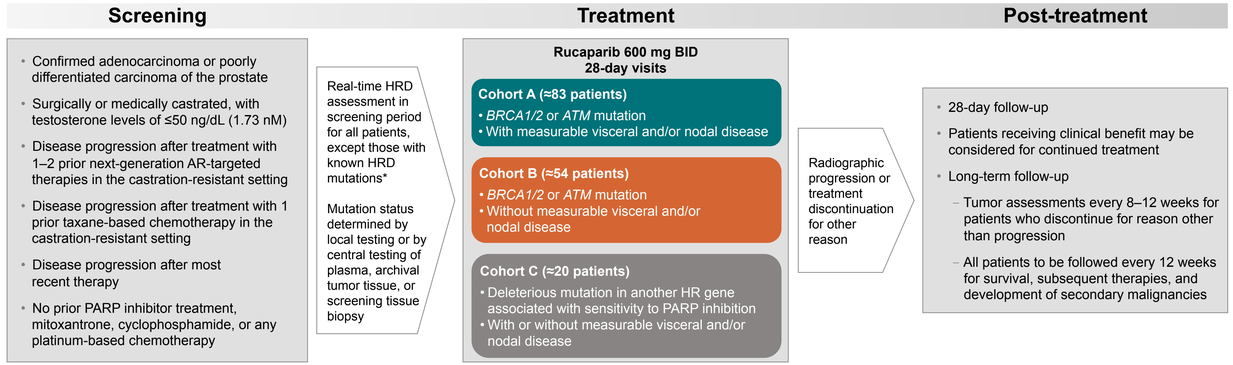
## INTRODUCTION

- Prostate cancer is the second-most common cause of cancer-related mortality in the United States, with approximately 30,000 deaths each year[1]
- The majority of prostate cancer deaths are associated with clinical progression to metastatic castration-resistant prostate cancer (mCRPC), a disease state characterized by resistance to standard androgen deprivation therapies
- Recently, several therapeutic modalities have been shown to provide a survival benefit for patients with mCRPC, including docetaxel, cabazitaxel, sipuleucel-T, radium Ra 223 dichloride, and 2 agents that target the androgen receptor (AR) pathway, abiraterone acetate and enzalutamide[2-6]
  - Abiraterone acetate and enzalutamide are often used as first-line therapies for mCRPC because of their tolerability and efficacy; patients who progress on AR-directed therapy may receive subsequent chemotherapy (eg, docetaxel plus prednisone)
- Despite clinical benefit from AR-directed therapy and chemotherapy, mCRPC patients eventually develop progressive disease, underscoring a need for novel therapies in this setting
- Germline and somatic mutations in *BRCA1*, *BRCA2*, and other homologous recombination (HR) DNA-repair genes have been identified in advanced prostate cancer (including mCRPC) at frequencies of 20%–25% or higher[7,8]
- Poly(ADP-ribose) polymerase (PARP) inhibitors are a promising class of agents that are synthetically lethal to cells with HR deficiency (HRD)
  - In a study of the PARP inhibitor olaparib, 14 of 16 patients with advanced mCRPC who responded to treatment had a tumor alteration in an HR gene, including *BRCA1*, *BRCA2*, *ATM*, and *PALB2*[8]
- These data provide a rationale for further investigation of PARP inhibitors, including rucaparib, in patients with mCRPC and alterations in HR genes

## TRITON2 TRIAL OVERVIEW

- TRITON2 is an international, multicenter (at least 100 sites will be selected), open-label phase 2 study evaluating rucaparib in patients with mCRPC associated with HRD, including in those with mutations in *BRCA1/2*, *ATM*, or other HR genes (**Figure 1**)
- Mutations in HR genes may have been previously identified by local testing (tumor tissue or blood) as documented in a patient's medical record, or by central testing on archival tumor tissue, screening tissue biopsy, and/or screening blood sample
- Patients will be allocated into cohort A, B, or C based on HR gene mutation and visceral disease status (**Figure 1**)
  - Planned enrollment is approximately 157 patients, with approximately 83 patients in Cohort A, 54 patients in Cohort B, and 20 patients in Cohort C
  - Cohorts A and B will employ a Simon 2-stage design requiring an objective radiographic response (by modified Response Evaluation Criteria In Solid Tumors version 1.1 ([RECIST]) in ≥9/37 and ≥4/19 patients, respectively, for continuation to stage 2; a futility rule will be implemented for Cohort C if enrollment of patients with an alteration in the same gene is much higher than anticipated
  - Cohort C will enroll patients with deleterious mutations in any of these genes: *BARD1*, *BRIP1*, *CDK12*, *CHEK2*, *FANCA*, *NBN*, *PALB2*, *RAD51*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L*. Compelling clinical/preclinical data suggests deleterious mutations in these genes may confer sensitivity to a PARP inhibitor
- Patients will receive a starting dose of rucaparib 600 mg twice daily (BID)
- Treatment will continue until:
  - Confirmed radiologic disease progression as assessed by investigator
  - Unequivocal clinical disease progression
  - Unacceptable toxicity or inability to tolerate further treatment
  - Loss to follow-up
  - Withdrawal of consent
- Patient safety will be evaluated throughout the trial
- TRITON2 will be conducted in accordance with Declaration of Helsinki, International Conference on Harmonisation Good Clinical Practice guidelines, and applicable regulatory requirements

### Figure 1. TRITON2 Study Design




*Patients with known HRD mutations are required to submit archival tumor tissue, if available; however, enrollment is not contingent on analysis.
AR, androgen receptor; BID, twice daily; HR, homologous recombination; HRD, homologous recombination deficiency; PARP, poly(ADP-ribose) polymerase.

## PATIENT ELIGIBILITY

### Table 1. Key Patient Inclusion/Exclusion Criteria

| Key Inclusion Criteria | Key Exclusion Criteria |
|---|---|
| • ≥18 years of age<br>• Histologically or cytologically confirmed adenocarcinoma or poorly differentiated carcinoma of the prostate<br>• Surgically or medically castrated, with serum testosterone levels ≤50 ng/dL (1.73 nM)<br>• ECOG Performance Status of 0 or 1<br>• Adequate organ function<br>• Evidence of disease progression after prior therapy for mCRPC, including:<br>– Treatment with 1–2 prior next-generation AR-targeted therapies (abiraterone acetate, enzalutamide, or investigational agent), and<br>– Treatment with 1 prior taxane-based chemotherapy<br>• Molecular evidence of mCRPC associated with HRD[a]:<br>– Cohort A and B: deleterious *BRCA1/2* or *ATM* mutation<br>– Cohort C: deleterious mutation in another HR gene associated with sensitivity to PARP inhibition<br>• Measurable visceral or nodal disease per RECIST in Cohort A only | • Prior PARP inhibitor treatment, mitoxantrone, cyclophosphamide, or platinum-based chemotherapy<br>• Initiated bisphosphonate or denosumab therapy or adjusted bisphosphonate or denosumab dose/regimen within 4 weeks prior to first rucaparib dose<br>• Symptomatic and/or untreated CNS metastases<br>• Active secondary malignancy, with the exception of curatively treated non-melanoma skin cancer, carcinoma in situ, or superficial bladder cancer<br>• Adverse effect of prior therapy not resolved to grade ≤1, with the exception of alopecia |

[a]Mutation status is determined by local testing (documented in the patient's medical record) or by the central testing of plasma, archival tumor tissue, or tissue biopsy performed during screening.
AR, androgen receptor; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; HRD, homologous recombination deficiency; mCRPC, metastatic castration-resistant prostate cancer; PARP, poly(ADP-ribose) polymerase; RECIST, Response Evaluation Criteria In Solid Tumors version 1.1.

## STUDY OBJECTIVES

### Primary Objectives

- Assess the efficacy of rucaparib based on the response rate in mCRPC patients with HRD who progressed on AR-targeted therapy (abiraterone acetate, enzalutamide, or investigational AR-targeted agent) and taxane-based chemotherapy in the castration-resistant setting
  - **Cohort A:** Primary endpoint is the centrally assessed objective response rate (ORR) defined as complete response (CR) or partial response (PR) using RECIST
  - **Cohort B:** Primary endpoint is locally assessed prostate-specific antigen (PSA) response (≥50% decrease)
  - **Cohort C:** Primary endpoint is centrally assessed ORR defined as CR or PR using either modified RECIST (if measurable visceral and/or nodal disease is present) or locally assessed PSA response (if visceral and/or nodal disease is absent)

### Secondary Objectives

- Assess radiologic progression-free survival, overall survival, clinical benefit rate, PSA response ≥50%, PSA response ≥90%, and time to PSA progression
- Characterize steady-state pharmacokinetics of rucaparib in patients with mCRPC
- Assess safety and tolerability of rucaparib

### Key Exploratory Objectives

- Evaluate patient-reported outcomes using the EQ-5D, Functional Assessment of Cancer Therapy–Prostate, analgesic drug score, and Brief Pain Inventory–Short Form
- Assess concordance in HR gene mutation status in matched screening biopsy tissue, archival primary tumor tissue, and plasma circulating tumor DNA (ctDNA)
- Assess ctDNA as a molecular marker of response and circulating tumor cell phenotype as a marker of response
- Evaluate loss of heterozygosity in metastatic disease site biopsy and archival primary tumor tissue samples
- Evaluate mechanisms of response and resistance in ctDNA and progression tumor tissue samples

## EVALUATIONS

### Efficacy Analyses

- Tumor assessments will be performed during screening (baseline), every 8 weeks up to 24 weeks, and every 12 weeks thereafter using appropriate imaging techniques
  - Soft-tissue (visceral and nodal) disease will be evaluated based on modified RECIST criteria
  - Bone lesions will be evaluated based on Prostate Cancer Clinical Trials Working Group 3 criteria
- PSA response will be evaluated by the local laboratory during screening (baseline), on day 1 of week 1, and every 4 weeks thereafter

### Safety Analyses

- Adverse events (incidence, type, seriousness, and severity), clinical laboratory parameters, vital signs, and electrocardiogram parameters will be assessed throughout the study
  - Adverse events will be graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.0

### Pharmacokinetic Evaluation

- Plasma samples will be collected 1 hour before rucaparib dose on day 1 of weeks 5, 9, 13, and 17

## PLASMA-BASED COMPANION DIAGNOSTIC

- TRITON2 will also explore the development of a diagnostic based on ctDNA from plasma
- A centrally based, retrospective analysis will be performed to determine the concordance between HR gene alterations identified in tumor tissue samples and ctDNA obtained from plasma
  - Tumor tissue samples may consist of a biopsy obtained during the screening period (encouraged, but not required) and/or archival tumor tissue (required where available)

## TRIAL SUMMARY

- Patients with mCRPC may harbor mutations in HR genes and could benefit from treatment with a PARP inhibitor such as rucaparib
- The phase 2 TRITON2 study aims to determine the response rate with rucaparib treatment in patients with mCRPC associated with HRD who progressed on both AR-targeted therapy and taxane-based chemotherapy
- Approximately 157 patients will be enrolled at more than 100 sites worldwide

## REFERENCES

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