INTRODUCTION

- Germline and somatic mutations in BRCA1, BRCA2, ATM, and other homologous recombination (HR) DNA-repair genes have been identified in advanced prostate cancer (including mCRPC) at frequencies of 20%–25% or higher.\(^1,2\)
- Poly(ADP-ribose) polymerase (PARP) inhibitors are a promising class of agents that are synthetically lethal to cells with HRD.\(^3\)
  - In preclinical studies, the PARP inhibitor rucaparib demonstrated potent cytotoxicity in prostate cancer cell lines with CRISPR-mediated knockout of BRCA2 or ATM.\(^6\)
  - In a phase 2 study of the PARP inhibitor olaparib (NCT01682772) in patients with mCRCP, 14 of 16 evaluable patients who had progressed on ≥ 1 prior chemotherapy and responded to olaparib treatment had a tumor alteration in an HR gene, including BRCA1, BRCA2, and ATM.\(^6\)
  - These data provide a rationale for further investigation of the PARP inhibitor rucaparib in patients with mCRCP and an alteration in an HR gene.

TRITON3 TRIAL OVERVIEW

- TRITON3 (CO-338-063; NCT02975934) is an international, multicenter, open-label, phase 3 study evaluating rucaparib 600 mg twice daily versus physician’s choice of abiraterone, enzalutamide, or docetaxel as treatment for patients with mCRCP who have a deleterious germline or somatic mutation in BRCA1, BRCA2, or ATM (Figure 1).

PATIENT ELIGIBILITY

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

**Key inclusion criteria**
- ≥ 18 years of age
- Histologically or cytologically confirmed adenocarcinoma or poorly differentiated carcinoma of the prostate
- Prostate-specific antigen (PSA) or clinically palpable, with serum testosterone levels of ≤ 50 ng/dL (1.73 nmol/L)
- Evidence of disease progression after treatment with 1 prior next-generation, AR-signaling directed therapy (abiraterone acetate, enzalutamide, or investigational agent) for castration-resistant disease (treatment with the older antiandrogen therapies, such as bicalutamide, flutamide, and nilutamide, are not counted toward this limit)
- BRCA1, BRCA2, or ATM mutation identified by local or central laboratory testing
- Eastern Cooperative Oncology Group Performance Status of 0 or 1

**Key exclusion criteria**
- Prior chemotherapy (eg, docetaxel, mitoxantrone, cyclophosphamide, or platinum-based agents) for mCRCP
- Prior PARP inhibitor treatment
- Initiated bisphosphonate or denosumab therapy or adjusted bisphosphonate or denosumab dose/ regimen within 4 weeks prior to first dose of rucaparib
- Symptomatic and/or untreated CNS metastases
- Active secondary malignancy, with the exception of curatively treated nonmelanoma skin cancer, carcinoma in situ, or superficial bladder cancer
- Received treatment with chemotherapy, hormonal therapy (with the exception of LHRH analog), radiation, antibody therapy, immunotherapy, gene therapy, angiogenesis inhibitors, or experimental drugs ≤ 14 days prior to first dose of study drug

*Patients with a known deleterious BRCA1, BRCA2, or ATM mutation (documented in the patient's medical record) who should also submit archival tumor tissue, if available; biopsy of visceral/nodal metastasis preferred.

**AR**: androgen receptor; **CNS**: central nervous system; **LHRH**: luteinizing hormone-releasing hormone; **mCRCP**: metastatic castration-resistant prostate cancer; **PARP**: poly(ADP-ribose) polymerase.

PLASMA-BASED COMPANION DIAGNOSTIC

- There are significant challenges in collecting and analyzing biopsy specimens from patients with mCRPC.
- TRITON3 will explore the use of circulating tumor DNA (ctDNA) purified from blood as a noninvasive companion diagnostic.
- Pretreatment blood samples will be collected from all patients and analyzed for BRCA1, BRCA2, and ATM mutations in ctDNA.
- A central retrospective analysis will be performed to determine the concordance between HR gene alterations identified in tumor tissue samples and ctDNA obtained from plasma.

TRIAL SUMMARY

- Deleterious mutations in BRCA1, BRCA2, and ATM have been identified in patients with mCRPC,\(^1,2\) and these patients could potentially benefit from treatment with a PARP inhibitor such as rucaparib.
- The TRITON3 phase 3 study aims to assess the efficacy of rucaparib vs physician’s choice of treatment for patients with mCRPC associated with HRD who progressed on prior androgen receptor–signaling directed therapy and have not received chemotherapy in the castration-resistant setting.
- TRITON3 is actively recruiting patients, with a goal of enrolling 400 patients from > 100 sites worldwide (Figure 2).
- Rucaparib is also being evaluated in the TRITON2 phase 2 study (NCT02952534), which will assess response to rucaparib in patients with mCRCP who have a deleterious germline or somatic BRCA1, BRCA2, or ATM mutation, and in an exploratory cohort of patients with an alteration in any of 12 additional prespecified HR genes (eg, RAD51C, RAD51D, or PALB2).

REFERENCEs


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