INTRODUCTION

- There are limited treatment options available for patients with mCRPC following androgen deprivation and taxane treatment.
- A deleterious germline and/or somatic mutation in *BRCA*1, *BRCA*2, *ATM*, or other homologous recombination (HR) DNA-repair gene is present in up to 25% of patients with advanced prostate cancer, including mCRPC.
- Poly(ADP-ribose) polymerase (PARP) inhibitors, such as rucaparib, have shown activity in tumors with HRD through synthetic lethality.
- TRITON2 (CO 2008) is actively recruiting patients, with a goal of enrolling approximately 160 patients from >100 sites worldwide (Figure 3).
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- Patients with mCRPC may harbor a deleterious mutation in *BRCA1*, *BRCA2*, or other HR gene and potentially benefit from targeted treatment with the PARP inhibitor rucaparib.

Figure 1. Rucaparib-Mediated Synthetic Lethality

<table>
<thead>
<tr>
<th>PARP inhibitor</th>
<th>BRCA protein loss</th>
<th>DNA damage repair deficiency</th>
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<tbody>
<tr>
<td>Rucaparib</td>
<td>BRCA deficiency</td>
<td>HRD</td>
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</table>

*TRITON2 TRIAL OVERVIEW*

- **TRITON2** (CO-338-052; NCT02952534) is an international, multicenter, open-label, phase 2 study evaluating rucaparib 600 mg twice daily in patients with mCRPC associated with HRD (Figure 2).
- Patients are being allocated into three cohorts based on HR gene status:**
  - **Cohort A (≈83 patients)**: Patients with *BRCA1*, *BRCA2*, *ATM*, or other HR gene mutation.
  - **Cohort B (≈20 patients)**: Patients with deleterious germline or somatic mutation in *BRCA1*, *BRCA2*, *ATM*, or other HR gene mutation.
  - **Cohort C (≈20 patients)**: Patients without HRD.

**PLASMA-BASED COMPANION DIAGNOSTIC**

- There are significant challenges in collecting and analyzing tumor tissue specimens from patients with mCRPC.
- **TRITON2** will explore the use of circulating tumor DNA (ctDNA) purified from blood as a companion diagnostic.
- Pretreatment blood samples will be collected from all patients and analyzed for *BRCA1*, *BRCA2*, *ATM*, and other HR gene mutations in ctDNA.
- A central retrospective analysis is planned to evaluate the agreement between HR gene alterations identified in tumor tissue specimens and ctDNA obtained from plasma.

**SPECIAL CONSIDERATIONS**

- Patients with an ovarian-recurrent BRCA1, BRCA2, or ATM mutation (documented in the patient's medical record) should also submit archival tumor tissue specimens from patients with mCRPC in an alter with an HR gene mutation.

**TRIAL SUMMARY**

- Up to 25% of patients with mCRPC may harbor a deleterious mutation in *BRCA1*, *BRCA2*, or other HR gene and potentially benefit from targeted treatment with the PARP inhibitor rucaparib.
- TRITON2 is actively recruiting patients, with a goal of enrolling approximately 160 patients from >100 sites worldwide (Figure 3).

**REFERENCES**

5. Lee CE, Bhatia R, Pathak S, et al. A central retrospective analysis is planned to evaluate the agreement between HR gene alterations identified in tumor tissue specimens and ctDNA obtained from plasma.