TRITON2: An International, Multicenter, Open-Label, Phase 2 Study of the PARP Inhibitor Rucaparib in Patients with Metastatic Castration-Resistant Prostate Cancer (mCRPC) Associated with Homologous Recombination Deficiency (HRD)

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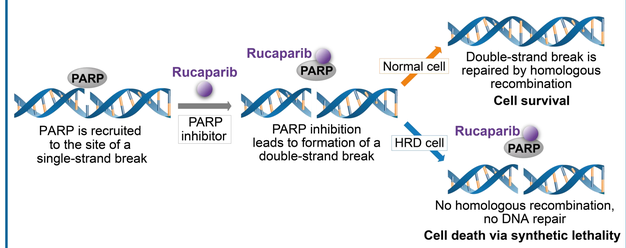
INTRODUCTION

- There are limited treatment options available for patients with mCRPC following androgen deprivation and taxane treatment
- A deleterious germline and/or somatic mutation in *BRCA1*, *BRCA2*, *ATM*, or other homologous recombination (HR) DNA-repair gene is present in up to 25% of patients with advanced prostate cancer, including mCRPC[1-3]
- Poly(ADP-ribose) polymerase (PARP) inhibitors, such as rucaparib, have shown activity in tumors with HRD through synthetic lethality (**Figure 1**)[4-6]
- PARP inhibitors have demonstrated preliminary evidence of antitumor activity in patients with sporadic mCRPC with an alteration in an HR gene[7]

Figure 1. Rucaparib-Mediated Synthetic Lethality

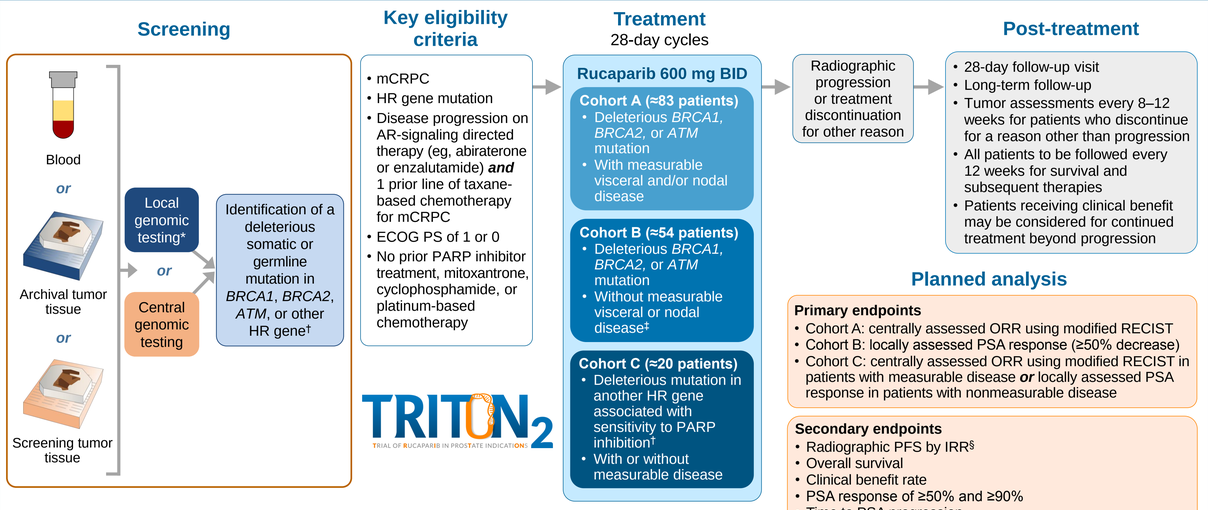


HRD, homologous recombination deficient; PARP, poly(ADP-ribose) polymerase.

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 cohort A, B, or C based on HR gene mutation and measurable disease status (**Figure 2**)
- Mutation in HR genes can be determined in various ways (**Figure 2**)

Figure 2. TRITON2 Trial Schema



*Patients with a known deleterious *BRCA1*, *BRCA2*, or *ATM* mutation (documented in the patient's medical record) should also submit archival tumor tissue, if available; tumor tissue samples of visceral/nodal metastasis preferred.
†*BARD1, BRIP1, CDK12, CHEK2, FANCA, NBN, PALB2, RAD51, RAD51B, RAD51C, RAD51D,* or *RAD54L*.
‡Patients without measurable disease must have PSA >2 ng/mL on the most recent measurement.
§Modified RECIST[8] criteria will be used to document radiographic response in soft-tissue (visceral and nodal) disease, and Prostate Cancer Clinical Trials Working Group guidelines version 3[9] criteria will be used to document radiographic progression of bone lesions.
AR, androgen receptor; BID, twice daily; ctDNA, circulating tumor DNA; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HR, homologous recombination; IRR, independent radiology review; mCRPC, metastatic castration-resistant prostate cancer; ORR, objective response rate; PARP, poly(ADP-ribose) polymerase; PFS, progression-free survival; PSA, prostate-specific antigen; RECIST, Response Evaluation Criteria In Solid Tumors version 1.1.

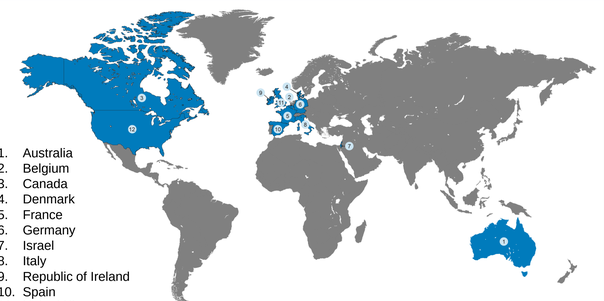
PLASMA-BASED COMPANION DIAGNOSTIC

- 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 (**Figure 2**)
- A central retrospective analysis is planned to evaluate the agreement between HR gene alterations identified in tumor tissue samples and ctDNA obtained from plasma

TRIAL SUMMARY

- Up to 25% of patients with mCRPC may harbor a deleterious mutation in *BRCA1*, *BRCA2*, *ATM*,[1-3] 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**)

Figure 3. Countries Participating in TRITON2



1. Australia
2. Belgium
3. Canada
4. Denmark
5. France
6. Germany
7. Israel
8. Italy
9. Republic of Ireland
10. Spain
11. United Kingdom
12. United States

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