The TRITON Clinical Trial Programme: Evaluation of the PARP Inhibitor Rucaparib in Patients with Metastatic Castration-Resistant Prostate Cancer (mCRPC) Associated with Homologous Recombination Deficiency (HRD)

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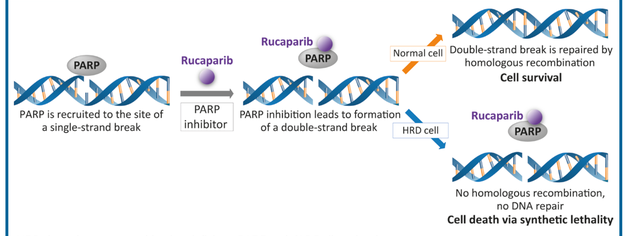
INTRODUCTION

- Recent data have shown that germline and somatic mutations in *BRCA1*, *BRCA2*, *ATM*, or other homologous recombination (HR) DNA-repair genes are present in patients with advanced prostate cancer (including mCRPC) at frequencies of 20%–25% or higher[1,2]
- These molecular markers may be used to select patients with mCRPC for targeted treatment with poly(ADP-ribose) polymerase (PARP) inhibitors
- PARP inhibitors, such as rucaparib, are a promising class of agents that are synthetically lethal to cells with HRD (**Figure 1**)[3-5]
  - In preclinical studies, rucaparib has demonstrated activity in prostate cancer cell lines with reduced levels of *BRCA2* or *ATM*[6]
  - In a phase 2 study of the PARP inhibitor olaparib (NCT01682772) in patients with mCRPC, 16 of 49 evaluable patients who had progressed on ≥1 prior chemotherapy responded to olaparib treatment; 14 of the 16 patients had a tumour alteration in an HR gene, including *BRCA1*, *BRCA2*, and *ATM*[2]
- These data provide a rationale for the TRITON clinical trial programme, which is investigating rucaparib in patients with mCRPC harbouring an alteration in an HR gene

Figure 1. Rucaparib-Mediated Synthetic Lethality



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

TRITON CLINICAL TRIAL PROGRAMME OVERVIEW

- **TRITON2 (CO-338-052; EudraCT 2016-003162-13; NCT02952534)** is a phase 2, international, multicentre, open-label study evaluating rucaparib 600 mg twice daily in patients with mCRPC associated with HRD, including those with a deleterious germline or somatic mutation in *BRCA1*, *BRCA2*, or *ATM*
- **TRITON3 (CO-338-063; EudraCT 2016-003163-20; NCT02975934)** is a phase 3, international, multicentre, open-label study evaluating rucaparib 600 mg twice daily vs physician's choice of abiraterone, enzalutamide, or docetaxel as treatment for patients with mCRPC that harbours a deleterious germline or somatic mutation in *BRCA1*, *BRCA2*, or *ATM*

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Figure 2. TRITON2 and TRITON3 Trial Schemas

TRITON2 — TRIAL OF RUCAPARIB IN PROSTATE INDICATIONS

Screening

Key eligibility criteria
- mCRPC
- Deleterious somatic or germline mutation in *BRCA1, BRCA2, ATM,* or other HR gene (see below) as determined by local testing,* analysis of screening tissue biopsy or archival tumour tissue,† or central testing of ctDNA from blood
- Disease progression on AR-signalling directed therapy (eg, abiraterone or enzalutamide) ***and*** 1 prior taxane-based chemotherapy for mCRPC
- ECOG PS of 1 or 0
- No prior PARP inhibitor treatment, mitoxantrone, cyclophosphamide, or platinum-based chemotherapy

Pretreatment blood samples will be collected from all patients for analysis of *BRCA1, BRCA2, ATM,* and other HR gene mutations in ctDNA

Other HR genes

BARD1	*FANCA*	*RAD51B*
BRIP1	*NBN*	*RAD51C*
CDK12	*PALB2*	*RAD51D*
CHEK2	*RAD51*	*RAD54L*

Treatment
28-day cycles

Rucaparib 600 mg BID

Cohort A (≈83 patients)
- *BRCA1, BRCA2,* or *ATM* mutation
- With measurable visceral and/or nodal disease

Cohort B (≈54 patients)
- *BRCA1, BRCA2,* or *ATM* mutation
- Without measurable visceral or nodal disease

Cohort C (≈20 patients)
- Deleterious mutation in another HR gene associated with sensitivity to PARP inhibition
- With or without measurable disease

Radiographic progression or treatment discontinuation for other reason

Post-treatment
- 28-day follow-up visit
- Long-term follow-up
  - Tumour assessments every 8–12 weeks for patients who discontinue for a reason other than progression
  - All patients to be followed every 12 weeks for survival, subsequent therapies, and development of secondary malignancies
- Patients receiving clinical benefit may be considered for continued treatment beyond progression

Planned analysis

Primary endpoints
- Cohort A: centrally assessed ORR using modified RECIST
- Cohort B: locally assessed PSA response (≥50% decrease)
- Cohort C: centrally assessed ORR using modified RECIST in patients with measurable disease ***or*** locally assessed PSA response in patients with nonmeasurable disease

Secondary endpoints
- Radiographic PFS by IRR‡
- Overall survival
- Clinical benefit rate
- PSA response of ≥50% and ≥90%
- Time to PSA progression
- Steady-state pharmacokinetics
- Safety and tolerability

TRITON3 — TRIAL OF RUCAPARIB IN PROSTATE INDICATIONS

Screening

Key eligibility criteria
- mCRPC
- Deleterious somatic or germline mutation in *BRCA1, BRCA2,* or *ATM* as determined by local testing,* analysis of screening tissue biopsy or archival tumour tissue,† or central testing of ctDNA from blood
- Disease progression after treatment with 1 prior next-generation, AR-signalling directed therapy (abiraterone, enzalutamide, or investigational agent) for mCRPC
- ECOG PS of 1 or 0
- No prior PARP inhibitor therapy
- No prior chemotherapy for mCRPC

Pretreatment blood samples will be collected from all patients for analysis of *BRCA1, BRCA2,* and *ATM* gene mutations in ctDNA

Treatment

Rucaparib 600 mg BID (n=267)

Randomisation 2:1

Physician's choice of (n=133):
Docetaxel (plus prednisone)
75 mg/m² every 21 days
(max 10 cycles)
OR
Abiraterone acetate (plus prednisone)
1000 mg QD
OR
Enzalutamide
160 mg QD

Radiographic progression or treatment discontinuation for other reason

Optional crossover
Patients who progress on comparator treatment may be considered for crossover to rucaparib

Post-treatment
- 28-day follow-up visit
- Long-term follow-up
  - Disease and PRO assessments every 8–12 weeks for patients who discontinue for a reason other than progression
  - All patients to be followed every 12 weeks for survival, subsequent therapies, and development of secondary malignancies
- Patients receiving clinical benefit with rucaparib may be considered for continued treatment beyond progression

Planned analysis

Primary endpoint
- Radiographic PFS by IRR‡

Key secondary endpoints
- ORR and DOR by modified RECIST in patients with measurable nodal/visceral disease
- Overall survival
- Clinical benefit rate
- PSA response of ≥50% and ≥90%
- Time to PSA progression
- PRO§
- Safety and tolerability

*Patients with a known *BRCA1, BRCA2,* or *ATM* mutation (documented in the patient's medical record). †All patients should submit archival tumour tissue (if available) for confirmatory testing by the central laboratory; biopsy of visceral/nodal metastasis preferred. ‡Modified RECIST[7] 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[8] criteria will be used to document radiographic progression of bone lesions. §Using the EQ-5D questionnaire,[9] Functional Assessment of Cancer Therapy–Prostate,[10] analgesic drug score, and Brief Pain Inventory Short Form[11] instruments.
AR, androgen receptor; BID, twice daily; ctDNA, circulating tumour DNA; DOR, duration of response; 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; PRO, patient-reported outcome; PSA, prostate-specific antigen; QD, once daily; RECIST, Response Evaluation Criteria In Solid Tumors version 1.1.

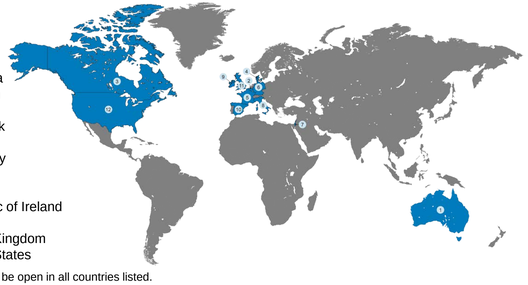
PLASMA-BASED COMPANION DIAGNOSTIC

- There are significant challenges in collecting and analysing biopsy specimens from patients with mCRPC
- The TRITON clinical trial programme will explore the use of circulating tumour DNA (ctDNA) purified from blood as a noninvasive companion diagnostic
- Pretreatment blood samples will be collected from all patients in both TRITON2 and TRITON3 and analysed 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 tumour tissue samples and ctDNA obtained from plasma

TRIAL SUMMARY

- Deleterious mutations in *BRCA1*, *BRCA2*, *ATM*, or other HR genes have been identified in patients with mCRPC,[1,2] and these patients could potentially benefit from treatment with the PARP inhibitor rucaparib
- The TRITON clinical trial programme is actively recruiting patients from >100 sites worldwide (**Figure 3**), with a goal of enrolling approximately 160 patients in TRITON2 and approximately 400 patients in TRITON3

Figure 3. Countries Participating in TRITON2 and TRITON3



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

Both trials will be open in all countries listed.

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