Trial of RucaparIb in ProsTate IndicatiONs 3 (TRITON3): An International, Multicenter, Randomized, Open-Label Phase 3 Study of Rucaparib vs Physician's Choice of Therapy for Patients with Metastatic Castration-Resistant Prostate Cancer (mCRPC) Associated with Homologous Recombination Deficiency (HRD)

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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[3-5]
  - 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 mCRPC, 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*[2]
  - These data provide a rationale for further investigation of the PARP inhibitor rucaparib in patients with mCRPC 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 vs physician's choice of abiraterone, enzalutamide, or docetaxel as treatment for patients with mCRPC who have a deleterious germline or somatic mutation in *BRCA1, BRCA2,* or *ATM* (**Figure 1**)

PATIENT ELIGIBILITY

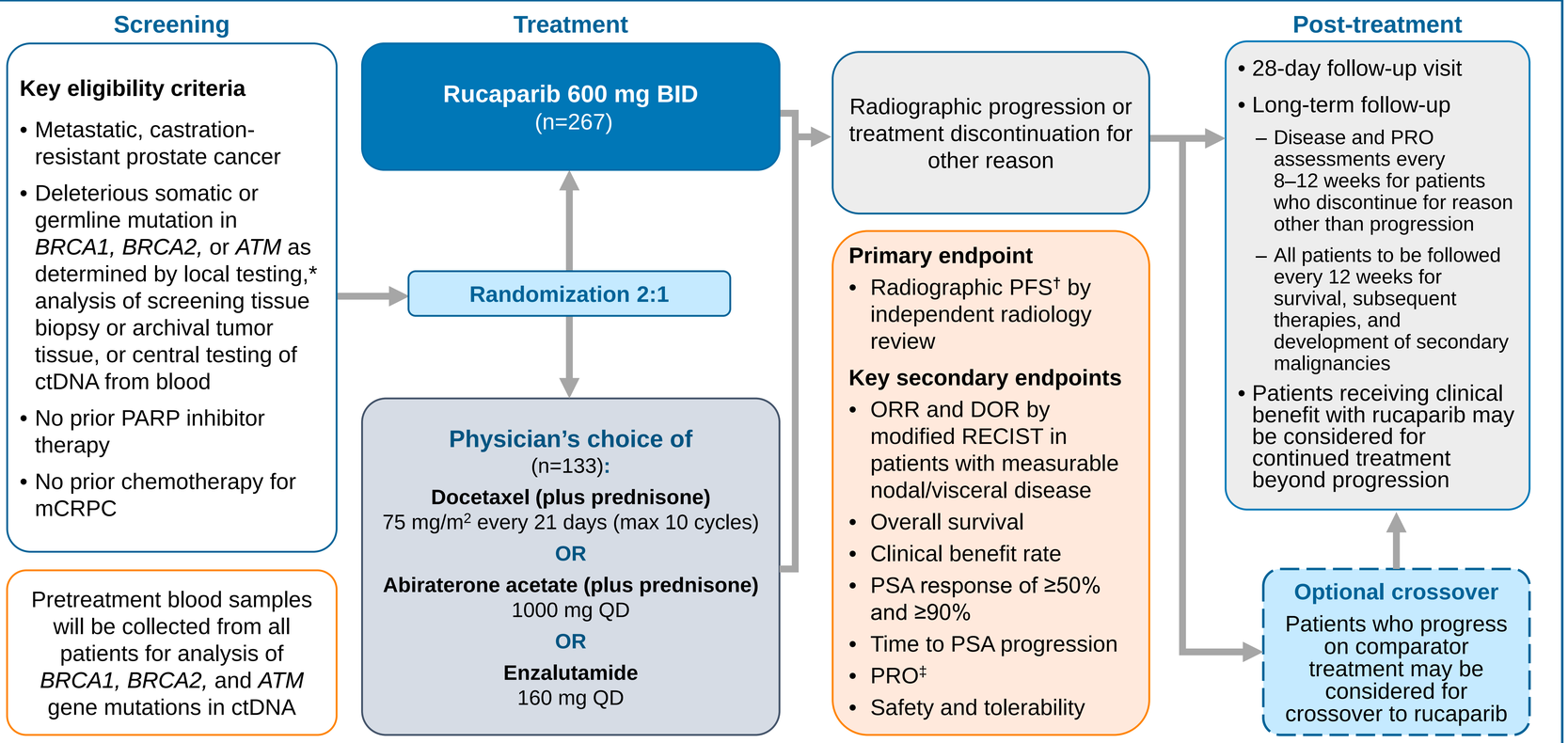
Table 1. Key Patient Inclusion/Exclusion Criteria

Key inclusion criteria
• ≥18 years of age
• Histologically or cytologically confirmed adenocarcinoma or poorly differentiated carcinoma of the prostate
• Surgically or medically castrated, with serum testosterone levels of ≤50 ng/dL (1.73 nM)
• 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* gene mutation identified by local or central laboratory testing[a]
• Eastern Cooperative Oncology Group Performance Status 0 or 1
Key exclusion criteria
• Prior chemotherapy (eg, docetaxel, mitoxantrone, cyclophosphamide, or platinum-based agents) for mCRPC
• 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

[a]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; biopsy of visceral/nodal metastasis preferred.

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

Figure 1. TRITON3 Trial Schema



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

†Modified Response Evaluation Criteria In Solid Tumors version 1.1 (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.

‡Patient-reported outcomes (PROs) using the EQ-5D questionnaire,[9] Functional Assessment of Cancer Therapy–Prostate,[10] analgesic drug score, and Brief Pain Inventory–Short Form[11] instruments.

BID, twice daily; ctDNA, circulating tumor DNA; DOR, duration of response; 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.

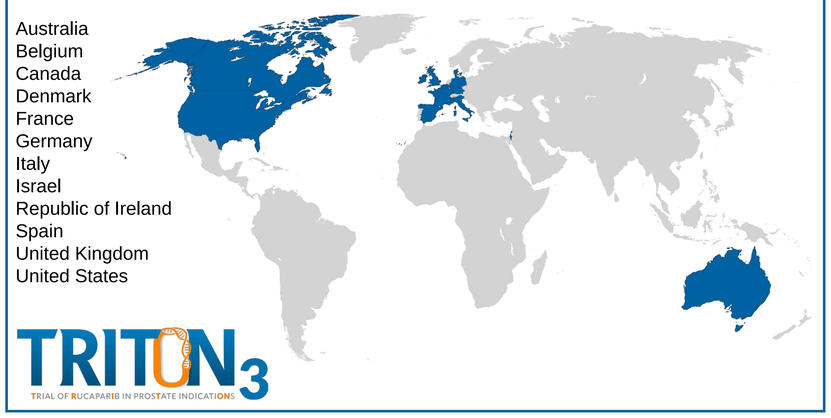
PLASMA-BASED COMPANION DIAGNOSTIC

- 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–signalling 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 mCRPC 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*)

Figure 2. Countries Participating in TRITON3



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