TRITON3: An International, Randomized, Open-Label, Phase 3 Study of the PARP Inhibitor 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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Background: Chemotherapy is the standard of care for mCRPC patients following progression on abiraterone or enzalutamide. However, recent data have shown that ≈20% of patients with mCRPC have a germline or somatic alteration in either BRCA1, BRCA2, or ATM (homologous recombination genes) (Robinson et al. Cell. 2015;161:1215-28), suggesting that these molecular markers may be used to select patients with mCRPC for targeted treatment with a poly(ADP-ribose) polymerase (PARP) inhibitor. PARP inhibitors are a promising class of agents that are synthetically lethal to cells with HRD. Preliminary evidence of PARP inhibitor antitumor activity has been demonstrated in patients with mCRPC and a homologous recombination gene mutation (Mateo et al. N Engl J Med. 2015;373:1697-708). Preclinical studies of rucaparib, a potent inhibitor of PARP1, PARP2, and PARP3, demonstrated potent cytotoxicity in BRCA2- or ATM-knockout prostate cancer cell lines. These data provide a compelling rationale for evaluating rucaparib in patients with mCRPC associated with HRD.

Methods: TRITON3 (NCT02975934) is a randomized, phase 3 study evaluating rucaparib 600 mg BID vs physician’s choice of therapy in patients with mCRPC and a deleterious germline or somatic BRCA1, BRCA2, or ATM mutation (per local and/or central testing). Patients must have progressed on androgen receptor signaling–directed therapy in the mCRPC setting; prior PARP inhibitor or chemotherapy for mCRPC are exclusions. Patients will be randomized 2:1 to rucaparib or physician’s choice of comparator therapy; patients randomized to physician’s choice may cross over to rucaparib upon radiographic progression confirmed by independent radiology review. The primary endpoint is radiographic progression-free survival (modified RECIST v1.1/PCWG3 criteria) confirmed by independent radiology review. Secondary endpoints include objective response rate, duration of response, patient-reported outcomes, overall survival, and safety. Pretreatment blood samples collected from all patients will enable development of a plasma-based companion diagnostic to select patients for rucaparib treatment. Patients (∼400) will be enrolled at >100 sites worldwide.

Results: TRITON3 is currently enrolling patients.

Conclusions: TRITON3 will assess the efficacy and safety of rucaparib treatment in patients with mCRPC associated with HRD.

Declaration of Interests:

CJR has served in a consulting or advisory role for Bayer and Millennium; has received honoraria from Janssen Oncology and Astellas Pharma; and has received research funding from BIND Biosciences, Karyopharm Therapeutics, and Novartis.

WA has served in a consulting or advisory role for Clovis Oncology; has received honoraria from Caret Healthcare; and has received research funding from AstraZeneca and Zenith Epigenetics.

RWG has served on speakers bureaus for Janssen Oncology.
DM has served in a consulting or advisory role and/or on speakers bureaus for Janssen, Dendreon, GenomeDx, Myriad, Pacific Edge Diagnostics, and Astellas; and has received support for scientific study or clinical trial from Janssen, Dendreon, Bayer, Myriad, Clovis Oncology, and Astellas.

HIS has served in a consulting or advisory role for AstraZeneca, Astellas Pharma, Bristol-Myers Squibb, Celgene, Endocyte, Exelixis, Endo Pharmaceuticals, Ferring, Foundation Medicine, Genentech, Janssen, OncologySTAT, Palmetto GBA, Pfizer, Sanofi, Takeda, Ventana Medical Systems, BIRB-Copernicus Group, and Medivation; has served on a speakers bureau for WebMD; has received financial support for travel and/or accommodation from Exelixis, Janssen, Sanofi, Endocyte, AstraZeneca, Genentech, Bristol-Myers Squibb, Celgene, Pfizer, Takeda, Ferring, WIRB-Copernicus Group, and Astellas Pharma; has received honoraria from Chugai Pharma; and has received research funding from BIND Biosciences, Exelixis, Janssen, Medivation, and Janssen Diagnostics.

SW, AS, LP, SS, and TG are employees of Clovis Oncology and may own stock or stock options in that company.

SC has served in a consulting or advisory role and/or on speakers bureaus for Clovis Oncology, Sanofi, Pfizer, Astellas Pharma, and Janssen; has received honoraria from GlaxoSmithKline and Novartis; and has received research funding from Sanofi and Johnson & Johnson.

All others have nothing to disclose.

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