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)

Charles J. Ryan,[1] Wassim Abida,[2] Alan Bryce,[3] Arjun Balar,[4] Igor Dumbadze,[5] Robert W. Given,[6] David Morris,[7] Daniel Petrylak,[8] Howard I. Scher,[2] Simon Watkins,[9] Andy Simmons,[9] Luke Passler,[9] Sanjay Shetty,[9] Tony Golsorkhi,[9] Simon Chowdhury[10]

[1]University of California, San Francisco, San Francisco, CA; [2]Memorial Sloan Kettering Cancer Center, New York, NY; [3]Mayo Clinic Arizona, Phoenix, AZ; [4]New York University Perlmutter Cancer Center, New York, NY; [5]The Urology Group, Cincinanati, OH; [6]Urology of Virginia, Virginia Beach, VA; [7]Urology Associates, PC, Nashville, TN; [8]Yale University - Yale Cancer Center, New Haven, CT; [9]Clovis Oncology Inc., Boulder, CO; [10]Guy's Hospital & Sarah Cannon Research Institute, London, UK

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 abiraterone, enzalutamide, or docetaxel 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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