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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Background: There are limited treatment options available for patients with advanced mCRPC following androgen deprivation and taxane treatment. Germline or somatic alterations in the homologous recombination genes BRCA1, BRCA2, and ATM have been observed in ≈20% of patients with mCRPC (Robinson et al. Cell. 2015;161:1215-28). These molecular markers are suggestive of HRD and may be used to select patients with mCRPC for targeted treatment with a poly(ADP-ribose) polymerase (PARP) inhibitor. PARP inhibition in cells with HRD results in synthetic lethality, and PARP inhibitors have demonstrated evidence of antitumor activity 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: TRITON2 (NCT02952534) is a phase 2 study evaluating rucaparib 600 mg BID in patients with mCRPC harboring a deleterious germline or somatic BRCA1, BRCA2, or ATM mutation (per local and/or central testing). An exploratory cohort is enrolling patients with an alteration in any of 12 other prespecified homologous recombination genes (eg, RAD51C, RAD51D, and PALB2). Patients must have progressed on androgen receptor signaling–directed therapy and 1 prior taxane-based chemotherapy for mCRPC. Patients who received prior treatment with a PARP inhibitor, mitoxantrone, cyclophosphamide, or platinum-based chemotherapy are excluded. The primary endpoint is response rate (per modified RECIST v1.1/PCWG3 in patients with soft-tissue disease and prostate-specific antigen response in patients with nonmeasurable disease). Secondary endpoints include duration of response, radiographic progression-free survival, overall survival, clinical benefit rate, 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 (≈160) will be enrolled at >100 sites worldwide.

Results: TRITON2 is currently enrolling patients.

Conclusions: TRITON2 will assess the efficacy and safety of rucaparib treatment in patients with mCRPC associated with HRD.

Declaration of Interests:

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.

AP has served in a consulting or advisory role for Janssen; and has received research funding from Bristol-Myers Squibb and GlaxoSmithKline.

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, Novartis.
SW, AS, JG, 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.

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.

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