A Phase 1/2 Study of Combination Olaparib and Radium-223 in Men with Metastatic Castration-Resistant Prostate Cancer with Bone Metastases (COMRADE).

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Background: Radium-223 is an α-emitting radioisotope that induces DNA double-stranded breaks leading to cell death and has demonstrated improvement in overall survival in men with metastatic castration-resistant prostate cancer (mCRPC) with bone metastases. PARP inhibitors, including olaparib and rucaparib, inhibit repair of DNA single-stranded beaks and have demonstrated clinical efficacy in mCRPC patients harboring alterations in the homologous recombination repair (HRR) pathway. In extensive preclinical cancer models, PARP inhibitors have shown efficacy as radiosensitizing agents. We designed a phase 1/2 trial to test the clinical hypothesis that the combination of radium-223 with olaparib will demonstrate anti-tumor activity in patients with mCRPC irrespective of underlying HRR deficiency status.

Methods: This is an open label, multi-center, phase 1/2 study (NCT03317392) evaluating the dosing, safety and efficacy of olaparib in combination with radium-223 in men with mCRPC with bone metastases. Patient must have 2 or more bone metastases and at least 1 bone metastasis that has not been treated with prior radiation therapy. Key exclusion criteria include the presence of visceral metastases or malignant lymphadenopathy exceeding 4 cm and prior therapy with radium-223 and/or PARP inhibitors. The phase 1 component of the study used a 3+3 dose escalation design to determine the recommended phase 2 dose of olaparib in combination with standard of care dosing of Radium-223. The primary endpoint of the phase 1 component is safety. The phase 2 component of the study is an open-label, randomized study evaluating the combination of olaparib and radium-223 compared to radium-223 alone. The primary endpoint of the phase 2 component is radiographic progression-free survival as defined by Prostate Cancer Working Group 3 guidelines for bone metastases and RECIST v1.1 for non-bone metastases. Secondary endpoints include time to PSA progression, PSA response, time to subsequent therapy, time to first skeletal event, overall survival, and safety. Exploratory endpoints include stratification of response based on HRR alterations, whole exome sequencing of plasma cell free DNA both at baseline, on treatment, and at progression, and evaluation of changes in the tumor immune microenvironment with therapy. As of October 1, 2020, the phase 1 component has completed accrual and we anticipate opening the phase 2 component by December 2020.