TPS5120 **Poster Session**

The impact of DNA repair genetic alterations identified by circulating tumor DNA on sensitivity to radium-223 in bone metastatic, castration-resistant prostate cancer.

Steven M. Blinka, Sarah K. Holt, Aaron Lin, Daniel M. Lim, Jorge Ramos, Thomas Murphy, Nathan Conrad, Chelsea Brammeier, Jarey Wang, John M. Floberg, Jessica E. Hawley, Heather H. Cheng, Todd Yezefski, Andrew Caleb Hsieh, Justin Thomas, Ana Ponce Kiess, Glenn Liu, Colin C. Pritchard, Evan Y. Yu; Fred Hutchinson Cancer Center, Seattle, WA; Department of Urology, University of Washington, Seattle, WA; University of Washington School of Medicine, Seattle, WA; Pfizer Inc., Bothell, WA; Bozeman Health Cancer Center, Bozeman, MT; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD; University of Wisconsin Carbone Cancer Center, Madison, WI; Division of Hematology & Oncology, University of Washington & Fred Hutchinson Cancer Center, Seattle, WA; University of Wisconsin Carbone Cancer Center, University of Wisconsin School of Medicine and Public Health, Madison, WI; Department of Laboratory Medicine and Pathology, University of Washington, Seattle, WA

Background: Selection, timing, and sequencing of therapy for men with bone metastatic castration-resistant prostate cancer (mCRPC) for optimal clinical outcomes is not well-defined. Accordingly, identification of predictive biomarkers for response and outcomes to a given therapy is critical to guide clinical decision-making. Prior research from our group and others has demonstrated that a high proportion (up to 25%) of mCRPC patients harbor aberrations in DNA damage repair (DDR) genes. These findings are clinically meaningful given the efficacy of PARP inhibitors in treating a subset of mCRPC patients with DDR defects. Radium-223 acts by delivering high-energy alpha particles selectively to bone metastases leading to double-stranded DNA breaks. Retrospective studies have shown patients with DDR alterations who are treated with radium-223 have overall survival benefit, improved alkaline phosphatase (ALP) response, and more commonly complete radium-223 treatment. Therefore, we hypothesize that mCRPC with alterations in DDR genes should be particularly vulnerable to treatment with radium-223 and should be evaluated for resultant outcomes prospectively. **Methods:** This Phase 2, multi-center, prospective single-arm biomarker trial aims to enroll 60 patients. Eligible patients must have mCRPC, radiographic evidence of bone disease, symptoms, and PSA ≥10 to ensure successful ctDNA analysis. All patients will receive radium-223 (55 kBq/kg) for up to 6 doses. Patients who have received prior platinum containing chemotherapy will be excluded. ctDNA will be obtained for OncoPlexCT to determine if a patient has a DDR gene alteration (results will not affect treatment plan). Leukocyte analysis will be performed to confirm whether specific alterations are germline vs somatic. The primary objective is to determine the response rate of bone mCRPC with DDR deficiency to treatment with radium-223. Response will be defined as having PSA and/or ALP decline of ≥30% from baseline. The null hypothesis is that the true response rate is 0.40, and the alternate hypothesis is the true response rate is 0.80 (TOPARP, NCT01682772). It is estimated that 25% of the patient population will have DDR alterations and outcomes will be compared with those who are DDR proficient. Using 90% power and an alpha of 0.05, we will accrue 60 patients to ensure the goal of 12 patients with DDR alterations is met. Secondary objectives include determining whether patients who received a prior PARP inhibitor have no decrement in response, overall survival, number of cycles of radium-223 received, and effect of germline vs somatic alterations on response. This trial is currently open to enrollment at Fred Hutch, University of Wisconsin, and Johns Hopkins, and 22/60 patients have already been enrolled. Clinical trial information: NCT04489719. Research Sponsor: Fred Hutch Cancer Center is the primary sponsor of this study. Bayer provided some financial support for this research.