

Impact of germline mutations in Homologous Recombination (HR) genes on the response to Radium-223 for metastatic castration resistant prostate cancer (mCRPC)

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BACKGROUND: Ra223 is a bone-seeking α -emitter targeted therapy that induces double-strand DNA breaks (DSBs). The HR pathway is used to accurately repair DSBs and a significant proportion of mCRPC patients harbor pathogenic germline HR mutations (gHR+). We hypothesize that gHR+ patients, with an impaired ability to repair DSBs, are more likely to respond to Ra223 than gHR- patients.

METHODS: This is an exploratory preplanned analysis of the PRORADIUM study (NCT02925702). PRORADIUM is a prospective observational biomarkers study of mCRPC patients treated with standard-of-care Ra223. Participants were screened for germline mutation in DNA damage and response genes using a multigene panel (*Castro et al. J Clin Oncol 2019*). Alkaline Phosphatase (ALP) response at 12 weeks was the primary endpoint. PSA response at 12 weeks, overall survival (OS) from Ra223 and clinical and/or radiographic progression free survival (PFS) were also analyzed.

RESULTS: 161 out of 168 patients enrolled in PRORADIUM with available germline testing results were included. A pathogenic gHR mutation was identified in 14 (8.7%) patients (*5 BRCA2, 4 ATM, 1 BRCA1, 1 BRCA1+CHEK2, 1 BRIP1, 1 NBN, 1 BLM*). Median age was 74 years (range 46-90). Performance status ECOG 1 was recorded in 91% pts. Median number of prior therapy lines for mCRPC was 2 (range 1-4) including at least one taxane in 63% patients. 54% of patients received 5 or 6 cycles of Ra223. After a median follow-up of 20 months, a $\geq 30\%$ decline in ALP at 12 weeks was observed in 75% of gHR+ compared to 43% of gHR- ($p=0.036$). No differences in PSA $\geq 50\%$ decline at 12 weeks (14% vs 8%, $p=0.437$) and PFS (4.5 vs 5.0 months, $p=0.670$) were observed by gHR status. A trend towards more prolonged OS from Ra223 was observed in gHR+ (median 14.4 vs 10.6 months, $p=0.066$).

CONCLUSIONS: In our study, germline HR mutations were associated with improved ALP response, suggesting a benefit from Ra223 in gHR+ patients.

CONFLICT OF INTERESTS: None

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