From Tumor Suppression to Bone Remodeling: The Dual Role of Ra-223 in Advanced Prostate Cancer

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Background Radium-223 dichloride (Ra-223) is a calcium-mimetic bone-targeting alpha-emitting radiopharmaceutical that prolongs overall survival and is FDA-approved for the treatment of castration-resistant prostate cancer bone metastases. This study investigates the effects of Ra-223 on skeletal parameters and transcriptional changes in both tumor and bone.

Methods We performed a preclinical study using patient-derived xenograft (MDA PCa PDX) obtained from prostate cancer bone metastasis that when applied *in vivo* mirrors the hallmark characteristics of bone-forming metastases observed in the clinic, reflecting the microenvironment-dependent nature of the disease. The treatment regimen consisted of two doses of Ra-223 or vehicle, followed by assessments of tumor volume by MRI, microCT, bone histomorphometry, and gene expression profiles by RNA sequencing and species-specific analysis to deconvolute the contributions of the tumor and stromal compartments.

Results Ra-223 treatment resulted in a significant reduction in tumor volume by MRI and altered bone architecture by microCT, compared with vehicle-treated controls. A significant decrease in osteoclast activity was observed in Ra-223-treated non-tumor-bearing bones compared to controls by histomorphometric analysis. Decreased osteoclast parameters were also exhibited in tumor-bearing bones, to a lesser degree. Gene set enrichment analysis highlighted significant differential expression in genes associated with metabolism and immune response in Ra-223-treated tumors and tumor-bearing bones, compared to controls. Transcriptome analysis of all compartments, tumor, tumor-bearing femurs and non-tumor bearing femurs showcased TP53 and MYC as central upstream regulators.

Conclusions The comprehensive multimodal analysis reveals the dual role of Ra-223 in modulating both the tumor and bone microenvironment transcriptionally, and by decreasing tumor volume while promoting bone remodeling. Ra-223 treatment has a significant effect on osteoclast activity, bone structure, and gene expression in both tumor-bearing and non-tumor-bearing bones. These results provide an understanding of Ra-223 modulating the bone environment and targeting metastatic prostate cancer lesions, accounting for its therapeutic efficacy in castration-resistant prostate cancer patients with skeletal metastases. Additional studies are necessary to investigate the long-term impact and clinical implications of these alterations.

Funding Acknowledgements. This work was supported in part by NCI/NIH U01 CA224044-05, the Prostate Cancer Foundation, DOD-PCRP (W81XWH-14-1-0554), the David H. Koch Center for Applied Research in Genitourinary Cancers at MD Anderson, Houston, TX, AGENCIA-PICT-RAICES-2018-02639 and PICT-2021-III-A-00080.

Conflicts of Interest Disclosure Statement. Authors declare no conflicts of interest.