

Studies to Evaluate the Immunologic Impact of Radium-223 in Patients with Prostate Cancer

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Background: Radium-223 has demonstrated an ability to improve survival in metastatic castration resistant prostate cancer (mCRPC). The primary understanding for its mechanism of action is related to DNA damage induced by alpha particles emitted once this infused radiopharmaceutical binds to areas in the bone with high turnover, such as metastatic sites of disease. Emerging data suggests that radiation can enhance immune recognition and immune cell killing of cancer cells through non-cytotoxic effects (immunogenic modulation).

Methods: This rationale formed the basis of a trial combining samarium-153 with immunotherapy (prostavac, a therapeutic cancer vaccine). In this study done prior to the approval of abiraterone or enzalutamide, men who had previously been treated with docetaxel were randomized to either samarium-153 alone or samarium-153 with immunotherapy.

Results: The findings of that study (n=44) suggested synergy with improved PFS and PSA responses when samarium-153 and immunotherapy were compared to samarium-153 alone (Heery et al. Oncotarget, 2016). The median PFS was 1.7 vs. 3.7 months in the samarium-153 alone and combination arms, respectively. (p = 0.041, HR = 0.51, P = 0.046). Preclinical data has also indicated that radium-223 has immunomodulatory effects on the tumor, inducing phenotypic changes rendering the cancer cells more susceptible to immune recognition and immune-mediated killing.

Conclusion: A better understanding of these immune effects in patients may allow the further optimization of radium-223 in the treatment of prostate cancer. Two planned studies at the NCI will investigate the immunologic impact of radium-223 in both the castration resistant and castration sensitive setting. One study in mCRPC will combine radium-223 either concurrently or sequentially with the anti-PD1 agent pembrolizumab. The primary endpoint of the trial will investigate changes in immunologic infiltration of the tumor microenvironment with both radium-223 alone and with the combination of radium-223 and pembrolizumab. Additional secondary endpoints will focus on changes in PDL1 expression, clinical responses, and immune responses seen in peripheral blood. A second trial in biochemically recurrent prostate cancer patients will evaluate patients that are bone scan and CT scan negative, but have positive findings on PET imaging (NaF or PSMA-based PET). This study will provide a unique opportunity to assess the immunologic impact in patients with prostate cancer who have normal testosterone. Furthermore, clinical and PET imaging responses will be evaluated in these patients with micro-metastatic disease.

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