Synergistic antitumor efficacy of radium-223 and enzalutamide in the intratibial LNCaP prostate cancer xenograft model.

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Background: Radium-223 dichloride (Ra-223) is a targeted alpha therapy that binds to newly formed bone matrix in bone metastases and induces DNA double-strand breaks in cancer cells, osteoblasts and osteoclasts. It is used for treating men with castration-resistant prostate cancer (CRPC) and bone metastases. Enzalutamide(enza) is a second-generation androgen receptor inhibitor also used for treating the same patient population, and the combination of Ra-223 and enza is currently being investigated in clinical trials. We evaluated the antitumor efficacy of Ra-223 and enza in the LNCaP intratibial model mimicking prostate cancer metastasized to bone. Previously, additive or synergistic antitumor effects were not observed when Ra-223 was combined with abiraterone and prednisone in the LNCaP model (Suominen et al., AACR 2020).

Methods: LNCaP prostate cancer cells were inoculated into the right tibia of male NOD.scid mice. The mice were randomized (n = 9/group) based on serum PSA and treated with vehicle, Ra-223 (330 kBq/kg, i.v., Q4W x 2), enza (30 mg/kg, p.o., QD) or with a combination treatment of Ra-223 and enza, for 28 days. Serum PSA levels were analyzed at the end of the study and compared to the pre-treatment levels. Serum bone formation and resorption biomarkers, PINP and CTX, respectively, were measured during the study. Tumor-induced abnormal bone area and Ra-223 uptake were determined by X-ray and gamma counter, respectively. The healthy tibiae were evaluated by microCT.

Results: Combination treatment showed synergistic antitumor efficacy as observed by lower PSA levels when compared to the vehicle, Ra-223 or enza monotherapies($p = 0.04$, $p = 0.008$ and $p = 0.002$, respectively). A statistical interaction betweenRa-223 and enza treatments was found ($p = 0.003$), confirming the synergistic effect. In combination treatment, the serum PSA change relative to pre-treatment levels was 18% of the vehicle. Accordingly, a decreasing trend ($p = 0.08$) in tumor-induced abnormal bone changes was associated with the combination treatment in the tumor-bearing tibiae (46% of the vehicle), whereas no changes in total bone structure/quality were observed in the healthy tibiae. Compared to monotherapies, the combination treatment had the most prominent lowering effect on the bone metabolism biomarkers PINP and CTX during the study. Concurrent administration of enza with Ra-223 did not affect Ra-223 uptake in tumor-bearing tibiae.

Conclusions: Compared to Ra-223 and enza monotherapies, the combination treatment demonstrated synergistic antitumor efficacy by decreasing PSA levels in the LNCaP intratibial model. Despite of prominent effects on tumor growth, the combination treatment was not observed to compromise bone health in the healthy tibiae. In conclusion, these preclinical results support the ongoing phase 3 trials PEACE III (NCT02194842) & ESCALATE (NCT04237584) of this combination.