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Background Prostate cancer is the second most common cancer and is one of the leading causes of cancer-related death among American men.¹ Prostate cancer exhibits significant tropism for the bone and once metastasis occurs, survival rates fall rapidly compared to primary tumors.² Bone metastasis can lead to bone loss and fractures which can severely compromise the patient's quality of life. Current treatment options are limited and focused on symptom management. Immune-based treatments are rapidly emerging as a possible therapeutic option for a variety of cancers including prostate cancer, however, patient sensitivity remains a concern. Chemotherapies such as cabozantinib have been shown to have immune-priming effects which can sensitize tumors to immunotherapies.³ Additionally, lower doses of chemotherapy can be used in this context which can reduce side effects. For this project, we hypothesized that a combination of chemotherapy (cabozantinib) and immunotherapy (Interleukin-27) could be effective in treating bone-metastatic prostate cancer and can help reverse some of the bone damage caused by the tumor. IL-27 is a multi-functional cytokine, which recruits immune cells to the tumor site, and promotes bone repair.⁴

Methods To test our hypothesis, we performed an in vivo experiment where syngeneic C57BL/6J mice were implanted with intratibial (cortical bone) TRAMP-C2ras tumors (TRAMP-C2 cells were infected with Lv-HrasG12V to make them more aggressive and gain the ability to grow in bone, and marked with Lv-Luc to follow tumor growth). Immunotherapy was administered in the form of sonoporation-assisted intramuscular gene delivery,⁴ with control (empty) vectors or vectors expressing mouse IL-27. Following immunotherapy, the animals received either cabozantinib (60 mg/kg) or vehicle control by oral gavage daily for two weeks. Bioluminescence imaging (BLI) was used to monitor Luc-expressing tumor size twice a week. Upon reaching a humane endpoint, the animals were euthanized, and tumor samples were harvested.

Results BLI showed that mice treated with a combination of IL-27 and cabozantinib had smaller tumor sizes compared to mice treated with individual treatments. The combination group had a significantly lower tumor burden compared to the control group. RNA sequencing was used to characterize changes in gene expression relating to the impact of therapeutics in signaling and cellular composition in the tumor microenvironment.

Conclusions We envision that chemo-immunotherapy approaches will emerge as a novel therapeutic strategy for treating bone-metastatic prostate cancer while reducing chemotherapy-associated toxicity, improving sensitivity to immunotherapy, and promoting healthy musculoskeletal tissue repair.

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