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Combination immunotherapy effective for advanced prostate cancer

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Advanced prostate cancer resistant to castration therapy appears to respond well to a combination of immune checkpoint blockades and treatments that target certain immune-busting cells commonly associated with poor patient prognosis and therapy resistance.

Researchers at The University of Texas MD Anderson Cancer Center developed a novel chimeric mouse model to test the combination therapy using immune checkpoint blockades with therapies targeting myeloid-derived suppressor cells (MDSCs). MDSCs are immune cells originating from bone marrow stem cells that possess strong immunosuppressive abilities and are known to play a role in tumor formation and metastasis. The team's findings were published in the March 9 online issue of *Nature*.

"A significant number of advanced prostate cancer patients treated with a chemical castration therapy called androgen deprivation therapy (ADT) experience relapse with relentless progression to lethal metastatic, castration-resistant prostate cancer," said Ronald DePinho, M.D., professor of Cancer Biology. "While immune checkpoint blockade therapy is effective in many cancers, it has been less successful for this particular form of prostate cancer, which has motivated a search for targeted therapies that overcome this resistance."

The investigation first tested anti-CTLA4 and anti-PD1 checkpoint blockades in combination, but found only "modest efficacy," said the paper's first author Xin Lu, Ph.D., formerly a DePinho trainee, now an

independent investigator at the University of Notre Dame. Targeted therapy using MDSC-inhibiting drugs, such as cabozantinib (Cabo) and BEZ, also demonstrated minimal anti-tumor capabilities. However, the combination of both therapeutic approaches proved successful.

"Strikingly, both primary and metastatic castration-resistant prostate cancer responded to a combined checkpoint blockade and MDSC targeted therapeutic approach," said DePinho. "These observations in mouse models of prostate cancer, using a sophisticated genetic approach developed by James Horner at MD Anderson, illuminate a clinical path hypothesis for combining immune checkpoint blockades with MDSC-targeted therapies in the treatment of this aggressive cancer."

DePinho added that clinical trials will be needed to substantiate the team's findings and to further explore the combination therapy with selective anti-androgen drugs for both established castration-resistant prostate cancer and newly diagnosed cases to achieve "durable clinical response."

Provided by University of Texas M. D. Anderson Cancer Center