

Combination immunotherapy benefits subset of patients with advanced prostate cancer

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Micrograph showing prostatic acinar adenocarcinoma (the most common form of prostate cancer) Credit: Wikipedia, [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

Results from a Phase II trial led by researchers at The University of Texas MD Anderson Cancer Center suggest that a combination of ipilimumab (anti-CTLA-4) plus nivolumab (anti-PD-1) can generate durable responses in a subset of patients with metastatic castration-resistant prostate cancer (mCRPC), an "immune-cold" cancer that does not typically respond well to immunotherapy.

In a cohort of patients without previous chemotherapy treatment, the overall response rate (ORR) was 25% and median overall survival (OS) was 19 months. In a post-chemotherapy cohort, the ORR was 10% and media OS was 15.2 months. Four patients (two in each cohort) achieved a complete response.

The results of the CheckMate 650 trial, published today in *Cancer Cell*, are the first report of [combination immune checkpoint inhibitors](#) in mCRPC. Early results from this study were presented at the 2019 American Society of Clinical Oncology Genitourinary Cancers Symposium. Based on the findings, alternate dosing regimens are now being evaluated in an expanded clinical trial to reduce treatment-related toxicities.

"Historically, prostate [cancer](#) has been very resistant to checkpoint inhibitors because it is immunologically cold with few tumor-infiltrating T cells," said principal investigator Padmanee Sharma, M.D., Ph.D., professor of Genitourinary Medical Oncology and Immunology. "These results suggest that a combination approach to increase T cell infiltration and then block inhibitory pathways may be a useful strategy for treating these patients. Going forward, we plan to optimize the schedule and dosing to improve the safety profile."

Designing a combination strategy

In previous research published in *Nature Medicine*, Sharma and colleagues discovered that prostate cancers deploy multiple mechanisms to dampen the anti-tumor immune response. Although anti-CTLA-4 therapy could recruit T cells, the tumor-infiltrating T cells elicited compensatory inhibitory pathways, including immune-suppressing proteins PD-L1 and VISTA.

This would explain why previous clinical trials evaluating single-agent

checkpoint inhibitors have not been effective in treating patients with mCRPC, said Sharma, who co-directs MD Anderson's immunotherapy platform, part of the institution's Moon Shots Program.

The researchers hypothesized that combining anti-CTLA-4 (ipilimumab) with anti-PD-1 (nivolumab) may be effective in bringing T cells into the tumor and overcoming the resulting immunosuppressive response.

The multi-institution, open-label study enrolled 90 men with mCRPC, who received the combination therapy every three weeks. Patients were enrolled in two cohorts: one with and one without prior chemotherapy. Participants were 77.8% Caucasian, 10% Black/African-American and 12.2% other.

In addition to response rates, the combination therapy achieved disease control in 46.9% and 13.3% of patients, with a median progression-free survival of 5.5 and 3.8 months in the pre- and post-chemotherapy cohorts, respectively.

Despite the positive responses, grade 3 and 4 treatment-related adverse events occurred in 42.2% of pre-chemotherapy patients and 53.3% of post-chemotherapy patients. The most common of these events was diarrhea, pneumonitis, colitis and increased lipase. Treatment-related adverse events led to discontinuation of therapy in a total of 31 patients. There were four treatment-related deaths, two in each cohort.

"There were patients who had clear benefit as a result of treatment, but there also were patients who had serious adverse events, which led us to amend the protocol to evaluate alternate schedules and doses and improve the safety of this approach," said Sharma.

Based on these data, the trial has been expanded to include more than 400 patients, with different dosing and schedules to identify strategies

that can improve efficacy and minimize toxicities.

Exploring biomarkers associated with response

The researcher team also conducted analyses to identify potential biomarkers associated with clinical outcomes in these patients.

While this study represents a small number of patients, their findings suggest that the combination may be more effective in patients with a relatively high tumor mutational burden (TMB). This is in agreement with previous work that suggests certain patients with mCRPC may respond to checkpoint blockade despite having low TMB relative to other cancers, such as melanoma and lung cancer.

"The current study represents the first step in trying to identify mCRPC patients who would benefit from combination therapy with ipilimumab plus nivolumab based on chemotherapy exposure as well as preliminary biomarker analyses," said co-author Sumit Subudhi, M.D., Ph.D., assistant professor of Genitourinary Medical Oncology. "The data generated to date are encouraging, but we clearly have more work to do in the expansion cohort as we try to administer effective combination strategies with fewer toxicities."

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

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