New Genetic Marker Linked to Improved Survival With Immunotherapy in Ovarian and Other Cancers

PPP2R1A mutations could be a valuable biomarker to help guide treatment and may offer a new therapeutic target.

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- Ovarian clear cell carcinoma is difficult to treat, and treatment options are limited
- Patients with specific PPP2R1A mutations in their tumors survived significantly longer after immunotherapy treatment
- Targeting PPP2R1A may improve responses even further according to laboratory studies
- PPP2R1A is an important predictive biomarker and possible treatment target for multiple cancer types, study found

Patients with ovarian clear cell carcinoma (OCCC) whose tumors have specific mutations in the PPP2R1A gene were found to have improved survival following immunotherapy compared to patients without these mutations, according to researchers from The University of Texas MD Anderson Cancer Center.

The findings, published today in Nature, suggest PPP2R1A mutations could be a valuable biomarker to help guide treatment for this difficult-to-treat ovarian cancer subtype and may offer a new therapeutic target to further improve outcomes in multiple cancer types.

Results of the study found that patients with PPP2R1A-mutant OCCC had a median overall survival (OS) of more than five years (66.9 months) after immunotherapy treatment, compared to just 9.2 months for patients without this mutation.

“Developing effective immunotherapies for ovarian cancer, including rare subtypes like ovarian

clear cell carcinoma, remains a significant unmet clinical need," said co-senior author Amir Jazaeri, MD, professor of Gynecologic Oncology and Reproductive Medicine. "Our study is the first to demonstrate the clinical importance of PPP2R1A mutations, and it opens the door to new strategies that could benefit many more patients."

In a Phase II trial, researchers investigated outcomes in a cohort of 34 patients with treatment-resistant OCCC who had been treated with a combination of immune checkpoint inhibitors – durvalumab and tremelimumab. Based on their findings in OCCC, experts also looked at two additional independent cohorts, one consisting of patients with endometrial cancer and the other including more than 9,000 patients with multiple cancer types who received immunotherapy treatment. Analyses confirmed the improved OS following immunotherapy in those with tumor PPP2R1A mutations.

In parallel, laboratory research showed that targeting PPP2R1A both in vitro and in vivo was also associated with improved response to immunotherapy, suggesting a causal link. This too indicates that therapies targeting PPP2R1A and the associated protein phosphatase 2A (PP2A) molecular pathway could be added to immunotherapy to further boost outcomes.

"Not only did we identify a new biomarker in ovarian cancer, but we also confirmed survival benefits in other cancer types," Jazaeri said. "Since PPP2R1A mutations are relatively uncommon, we believe the same benefits may be possible by targeting the PPP2A pathway --using drugs, and we currently are evaluating this in a clinical trial at MD Anderson."

The study represents an ongoing collaboration across multiple disciplines, led by co-senior authors Jazaeri; Linghua Wang, MD, PhD, associate professor of Genomic Medicine and associate member of the James P. Allison Institute and focus area co-lead with the Institute for Data Science in Oncology; and Rugang Zhang, PhD, chair of Experimental Therapeutics.

This research was co-lead by first authors Yibo Dai and Minghao Dang, PhD, of the Wang laboratory; Anne Knisely, MD, fellow in Gynecologic Oncology and Reproductive Medicine; and Mitsutake Yano, MD, PhD, postdoctoral fellow in the Zhang laboratory. A full list of collaborating authors and their disclosures can be found in the paper.

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