Novel ADC and immunotherapy combo shows promise in endometrial cancer subtype

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In a small, investigator-initiated Phase II study by Dana-Farber Cancer Institute investigators, a novel combination of an antibody-drug conjugate and an immune checkpoint inhibitor showed notable activity

in pre-treated patients with a difficult-to-treat form of endometrial cancer. In this study, tumors were reduced in six out of 16 patients treated with the combination, including one case in which the cancer disappeared.

The study tested mirvetuximab soravtansine and pembrolizumab in patients with folate receptor-α (FRα) positive recurrent microsatellite stable (MSS) / mismatch repair proficient (pMMR) serous endometrial cancer. The study met its primary endpoint, and the results support continued study of the combination.

"This is a really encouraging response rate," said principal investigator Rebecca Porter, MD, Ph.D., a medical oncologist in the Gynecological Oncology Program of Dana-Farber's Susan F. Smith Center for Women's Cancers.

"This study underscores the potential benefits of combining antibody drug conjugates with immunotherapies for this patient group."

Porter presents results of this study at the American Association for Cancer Research (AACR) Annual Meeting on Sunday, April 7, in San Diego, Calif.

Serous endometrial cancers make up approximately 5% of endometrial cancer cases, but account for about 40% of deaths from the disease. It is an aggressive subtype with poor outcomes.

About 30% of patients with serous endometrial cancer have tumors that express FRα, the target of mirvetuximab soravtansine, an antibody-drug conjugate (ADC). ADCs work by pairing a potent anti-cancer drug with an antibody that directs the drug to cells that express a certain marker, such as FRα.

In earlier work, it was shown that serous endometrial cancers likely have the highest expression of FRα, which provided the rationale to focus on this population in the current study.

In this study, Porter and colleagues opted to combine the ADC with pembrolizumab, an immune checkpoint inhibitor (ICI), based on preclinical evidence suggesting the two might be synergistic. ICIs release the brakes on the immune system so anti-tumor T cells can attack the cancer.

They don't tend to be active in MSS/pMMR serous endometrial cancer on their own. But preclinical evidence suggests that the ADC can alter immune cells in the tumor microenvironment in ways that could increase T cell infiltration into the tumor and enhance the effects of the ICI.

"We had a strong rationale for the combination and hoped it would be better than either drug alone," Porter said.

Porter and colleagues designed the two-stage trial as a single arm study in which all patients receive the same treatment. The first stage recruited 16 patients with recurrent or persistent FRα positive, MSS/pMMR serous endometrial cancer who were previously treated with one to four lines of therapy. The second stage would proceed to enroll additional patients if there were at least two objective responses or two cases of six-month, progression-free survival in the first stage.

In the first 16 patients treated, 37.5% of patients achieved an objective response. One patient achieved a complete response, and an additional five patients had a partial response. Five additional patients had stable disease. Therefore, the trial met its primary endpoint for both stages with more than four objective responses. Furthermore, two patients were progression-free for more than six months, one of them for nearly 12 months and the other for over 18 months.

"Almost two-thirds of these patients had three or four lines of therapy, so these results are notable," Porter said. "Some of these responses are what we would call exceptional."

Porter has also observed that some patients are progressing sooner than others. She and her team will be doing additional analyses to determine if there are molecular changes in the tumors or features of the microenvironment that can predict either response or resistance to the combination.

"Our next steps are to dive deeper into the potential mediators of the differences in response we're seeing," Porter said. "Our goal is to improve the duration of response for those who do respond to the combination."

Provided by Dana-Farber Cancer Institute

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