New Combo Shows Promise as Treatment for Advanced Bladder Cancer

Enfortumab vedotin plus Keytruda yielded a confirmed response in 71% of participants.

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Seattle Genetics and Astellas Pharma's enfortumab vedotin in combination with Merck's Keytruda (pembrolizumab) proved safe and showed encouraging clinical activity as a treatment for advanced bladder cancer. These findings from an ongoing Phase Ib trial of the combination were presented at the recent European Society for Medical Oncology Congress (ESMO 2019) in Barcelona.

The EV-103 trial is a multi-cohort, open-label, multicenter trial of enfortumab vedotin either alone or in combination with Keytruda. The study is evaluating the safety, tolerability and efficacy of the treatment in people with muscle-invasive, locally advanced or metastatic urothelial cancer.

Urothelial cancer involves the bladder in 90% of cases, but it can also occur in the urethra, ureters (the ducts through which urine passes from the kidneys to the bladder) and part of the kidneys. The recommended first-line treatment is platinum-based chemotherapy using cisplatin. Those who are unable to use cisplatin—for example, because they are too frail to tolerate it—can try checkpoint inhibitor immunotherapy, but a majority do not respond.

"Advanced urothelial cancer is an aggressive disease for which more options are needed, especially for patients who are ineligible for first-line treatment with cisplatin," Christopher J. Hoimes, DO, director of genitourinary oncology at the Case Comprehensive Cancer Center in Cleveland, said in a Seattle Genetics press release.

Enfortumab vedotin is a first-in-class antibody-drug conjugate that targets nectin-4, a protein present on nearly all urothelial tumor cells that is associated with the development and growth of cancer.

Keytruda is a checkpoint inhibitor that helps the immune system fight cancer. It blocks the PD-1 immune checkpoint receptor on T cells, which play a role in regulating immune function. Some tumors can hijack PD-1 to turn off immune responses against them. Drugs that block PD-1 or its binding partner, known as PD-L1, can essentially release the brakes and restore T-cell activity.

The participants in the analysis of the EV-103 trial presented at ESMO were receiving treatment for the first time and were ineligible for cisplatin-based chemotherapy. Eighty percent were men, and the median age was 69. They received treatment in 21-day cycles, receiving an intravenous infusion of enfortumab vedotin on days 1 and 8 and Keytruda on day 1. They were treated for a median of seven cycles.

At the time of the analysis, 45 participants, including five from a dose-escalation cohort (designed to determine the best dose of the new drug) and 40 from a dose-expansion cohort (a larger group receiving the selected dose), had been treated with the two drugs.

Seventy-one percent (32 of 45) of the participants experienced shrinkage of their tumors, otherwise known as an objective response to treatment. Thirteen percent (6 of 45) experienced a complete response, and 58% (26 of 45) experienced a partial response. Another 22% (10 of 45) had stable disease without further progression. Twenty-two of the responders were still on treatment.

Just over half of the participants (23 of 45) experienced severe adverse health events (Grade 3 or higher). The most frequent such event was an increase in lipase (a sign of pancreatitis), which occurred in 13% (6 of 45) of the participants. Eleven percent (5 of 45) experienced severe immune-mediated events, a side effect of checkpoint inhibitors.

Nine percent (4 of 45) of the participants discontinued therapy because of treatment-related adverse events, most commonly peripheral sensory neuropathy, which often causes weakness, numbness and pain in the hands and feet. One participant died of multiple organ dysfunction syndrome, which was deemed possibly related to treatment.

“These data are encouraging and support further exploration of a potential platinum-free combination of pembrolizumab and the investigational agent enfortumab vedotin,” said Roger Dansey, MD, chief medical officer at Seattle Genetics.

Other cohorts of the EV-103 study are evaluating enfortumab vedotin in combination with chemotherapy. The Food and Drug Administration is currently reviewing a new drug application for enfortumab vedotin alone for the treatment of people with locally advanced or metastatic urothelial cancer who were previously treated with a checkpoint inhibitor and platinum-based chemotherapy .

To read a press release about the study, click here.

To learn more about bladder cancer, click here.

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