Padcev Combo Continues to Show Promise for Advanced Bladder Cancer

Updated study results show antibody-drug conjugate plus Keytruda shrinks tumors in 73% of patients.

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Padcev (enfortumab vedotin), an antibody that delivers chemotherapy to tumors, continues to show durable benefit when combined with the checkpoint inhibitor Keytruda (pembrolizumab) in people with advanced bladder cancer, according to study results presented at the American Society of Clinical Oncology Genitourinary Cancers Symposium last week in San Francisco.

Nearly three quarters of participants in a Phase I/II study experienced complete or partial tumor shrinkage, with a majority of responses ongoing for nearly a year. It is still too early to determine whether the combination will prolong overall survival, but 82% of participants were alive after a year on treatment.

Jonathan Rosenberg, MD, of Memorial Sloan Kettering Cancer Center in New York, presented the latest findings from Study EV-103, evaluating Padcev plus Keytruda as a first-line treatment for locally advanced or metastatic urothelial cancer.

Urothelial cancer involves the bladder in 90% of cases, but it can also occur in other parts of the urinary tract. The standard initial treatment is platinum-based chemotherapy, but those who are unable to use cisplatin have poor outcomes. Checkpoint inhibitor immunotherapy is also an option, but a majority of patients do not respond.

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.

This analysis included 45 participants, 80% of them men, with a median age of 69 years. They were receiving treatment for the first time and were ineligible for cisplatin chemotherapy. Over 90% had cancer that had spread to their abdominal organs, including 33% with liver metastasis.

All participants in this nonrandomized trial received Padcev on days 1 and 8 and Keytruda on day 1 in three-week cycles, both administered by IV infusion. They received a median of nine cycles of treatment.

Padcev, from Astellas and Seattle Genetics, is an antibody-drug conjugate (ADC) that uses a monoclonal antibody to deliver a lethal drug to tumors. The antibody portion targets nectin-4, a protein found at high levels on most urothelial cancer cells.

Keytruda, from Merck, is a checkpoint inhibitor that helps the immune system fight cancer. It blocks the PD-1 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 release the brakes and restore T-cell activity. People with higher PD-L1 levels in their tumors tend to respond better to this type of treatment.

Padcev was approved by the Food and Drug Administration in December based on an earlier study showing that the ADC alone led to a 44% overall response rate, meaning complete or partial tumor shrinkage, in people previously treated with cisplatin and a checkpoint inhibitor.

But the treatment may work better when combined with immunotherapy from the outset, the approach used in Study EV-103. Initial results were presented at the European Society for Medical Oncology Congress in the fall, showing that 71% of people treated with Padcev plus Keytruda experienced tumor remission, including 13% with complete responses. Another 22% had stable disease without further progression.

In the latest analysis, the overall response rate rose to 73%, including 16% with complete responses. All but three participants (93%) experienced some degree of tumor reduction, though those with less than 30% shrinkage were classified as stable disease rather than response. Antitumor activity was observed regardless of PD-L1 levels, Rosenberg noted.

Treatment response was rapid, with 88% of responses occurring by the time of the first scan at around two months. After a median follow-up period of 10.4 months, the median duration of response had not yet been reached. Among the 33 responders, 18 (55%) were still responding, 11 (33%) had progressed and four (12%) had started a new treatment.

The median progression-free survival (PFS) time, meaning patients were still alive without worsening of their disease, was 12.3 months. The median overall survival (OS) time was not reached because most were still alive. At 12 months, the PFS rate was 50% and the OS rate was 82%.

“Cisplatin-based chemotherapy is the standard treatment for first-line advanced urothelial cancer; however, it isn’t an option for many patients,” Rosenberg said in a Seattle Genetics press release. “I’m encouraged by these interim results, including a median progression-free survival of a year for patients who received the platinum-free combination of Padcev and pembrolizumab in the first-line setting.”

Treatment was generally safe, but side effects were common. The most common treatment-related adverse events were fatigue, hair loss, peripheral neuropathy (nerve damage) and diarrhea. Over half (58%) experienced severe (Grade 3 or higher) side effects, the most common of which was elevated lipase, at 18%. Seven people (16%) had treatment-related serious adverse

events, including one who died of multiple organ failure. Six people (13%) stopped treatment because of side effects, three of them due to neuropathy.

Checkpoint inhibitors can lead to strong immune activation that harms healthy organs. Eight people (18%) experienced severe immune-mediated adverse events that required management with steroids. Rosenberg noted that rates of peripheral neuropathy, rash and hyperglycemia were similar to those seen with Padcev alone, and there were “no new safety signals” related to the combination.

While these results are promising, larger randomized studies are needed to show whether Padcev plus Keytruda does in fact work better than standard first-time treatment—especially in terms of overall survival—considering that this would be a “shockingly expensive combination” that could yield “shockingly good results,” Rosenberg said.

These findings also suggest that the combination might be beneficial for a larger group of patients, not just those who are ineligible for platinum-based chemotherapy. The Phase III EV-302 trial (ClinicalTrials.gov number NCT04223856) will compare Padcev plus Keytruda, with or without chemotherapy, versus platinum (cisplatin or carboplatin) and gemcitabine chemotherapy alone.

Click here to read the study abstract.

Click here to learn more about bladder cancer.
