Keytruda-Padcev Combo Boosts Survival for Bladder Cancer Patients

A chemotherapy-free regimen combining immunotherapy with an antibody-drug conjugate extended survival by 15 months.

October 26, 2023 By Liz Highleyman

Adding the checkpoint inhibitor Keytruda (pembrolizumab) to the antibody-drug conjugate Padcev (enfortumab vedotin) improved overall survival by more than 50% compared with chemotherapy for previously untreated people with locally advanced or metastatic bladder cancer, according to late-breaking study results presented at the European Society for Medical Oncology (ESMO) Congress.

"These results, showing a 53% reduction in the risk of death for the combination compared to chemotherapy, are striking and may open a new chapter for the treatment of these patients diagnosed with advanced urothelial carcinoma, who face an urgent need for new therapies," said Thomas Powles, MD, of Barts Cancer Centre at Queen Mary University of London, whose presentation earned a standing ovation.

Enfortumab vedotin & Pembrolizumab improving PFS & OS by 55% & 53% respectively compared to platinum based chemo in 1st line UC (+avelumab in 30%). Chemo has not been beaten before (despite multiple efforts). RR and CR of 68% & 29% is hard to beat. DOR not reached (1/3)#ESMO2023 pic.twitter.com/JyG38DiWi2

— Tom Powles (@tompowles1) October 22, 2023

Urothelial cancer affects the lining of the urinary tract. In about 90% of cases, it involves the bladder, but it can also occur in the urethra, ureters (the ducts from the kidneys to the bladder) and the lower part of the kidneys. More than 80,000 people in the United States will be diagnosed with bladder cancer this year, about 10% of whom will already have locally advanced or metastatic cancer at the time of diagnosis. The standard of care for first-line treatment of inoperable (unresectable) or metastatic urothelial cancer is platinum-based chemotherapy such as cisplatin.

The Phase III KEYNOTE-A39/EV-302 trial (NCT04223856) evaluated Keytruda plus Padcev versus chemotherapy as a first-line treatment for patients with locally advanced or metastatic urothelial cancer.

Keytruda is an immune checkpoint inhibitor that blocks the PD-1 receptor on T cells. Some tumors can hijack PD-1 to turn off immune responses. Drugs that block the interaction between PD-1 and its binding partner, known as PD-L1, can release the brakes and restore T-cell activity. Tumors with a higher PD-L1 expression level tend to respond better to this type of treatment.

Padcev is an antibody-drug conjugate, a monoclonal antibody targeting nectin-4 (a protein found on most urothelial cancer cells) that carries a potent chemotherapy drug that halts cell division. Prior studies showed that Padcev works well for advanced bladder cancer patients who were previously treated with both platinum chemotherapy and a checkpoint inhibitor and for those who were ineligible for cisplatin and had received only a checkpoint inhibitor.

KEYNOTE-A39/EV-302 enrolled 886 patients, a majority of whom were eligible for cisplatin or carboplatin chemotherapy, who could have any PD-L1 expression level. About three quarters were men, a majority were white and the median age was 69 years.

The participants were randomly assigned to receive Keytruda plus Padcev or a chemotherapy regimen consisting of cisplatin or carboplatin and gemcitabine. All drugs were administered by IV infusion in three-week cycles. Keytruda was given for a maximum of 35 cycles, Padcev for an unlimited number of cycles and chemotherapy for a maximum of six cycles. Participants and their providers knew which regimen they received.

The primary study endpoints were progression free survival—meaning patients were still alive without worsening disease—and overall survival. Progression-free survival was twice as long with the Keytruda-Padcev combination compared with chemotherapy (12.5 months versus 6.3 months). Likewise, overall survival was 31.5 months with the combination versus 16.1 months with chemotherapy, a 53% reduction in the risk of death.

The results were consistent across subgroups, including people who were not be eligible for cisplatin, those with low PD-L1 expression levels and those whose cancer had spread to the liver or other visceral organs.

“We’ve never before seen a survival signal in [previously treated] urothelial cancer,” Knowles noted. “We’ve never beaten chemotherapy in the first-line setting.”

Another study presented at the same session shares this distinction. In the CheckMate-901 trial (NCT03036098), adding the checkpoint inhibitor Opdivo (nivolumab) to cisplatin-gemcitabine chemotherapy also extended survival compared with chemotherapy alone, but by a more modest three months (21.7 months versus 18.9 months, representing a 22% reduction in the risk of death). These results were published last week in The New England Journal of Medicine. In prior studies, neither Keytruda nor Tecentriq (atezolizumab) significantly improved overall survival when added to chemotherapy for previously untreated bladder cancer patients.

Knowles also reported statistically significant improvements in secondary end-points. The overall response rate (tumor regression) was 68% in the Keytruda-Padcev arm versus 44% in the chemotherapy arm; 29% and 13%, respectively, had a complete response. The median duration of response was seven months in the chemotherapy arm but was not reached in the Keytruda-Padcev arm because a majority of patients were still responding.

Treatment was generally safe, though side effects were common in both groups and consistent with those seen in previous trials of these medications. More than half (56%) of people who received Keytruda-Padcev and 70% of those who received chemotherapy had severe (grade 3 or higher) treatment-related adverse events; 22% and 14%, respectively, stopped treatment due to adverse events. The most common severe side effects in the Keytruda-Padcev group were skin rash, peripheral neuropathy, hyperglycemia, diarrhea and low red and white blood cell counts (anemia and neutropenia).

Discussing the study findings, Andrea Apolo, MD, of the National Cancer Institute, said that Keytruda plus Padcev is “a new standard of care” for the first-line treatment of advanced or metastatic urothelial carcinoma. Challenges include managing the side effects of combination therapy and learning why the two drugs work so well together.

Merck (which makes Keytruda) and Seagen/Astellas (the makers of Padcev) plan to submit these findings to regulators to confirm the Food and Drug Administration’s accelerated approval of the combination for people ineligible to receive cisplatin and to request approval in other countries.

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