Keytruda Improves Long-Term Survival for People With Bladder Cancer

Patients treated with immunotherapy had a 30 percent reduction in the risk of death.

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The PD-1 checkpoint inhibitor Keytruda (pembrolizumab) led to a sustained improvement in overall survival for bladder cancer patients followed for two years, according to study results presented at the American Society of Clinical Oncology (ASCO) Genitourinary Cancers Symposium last week in San Francisco.

Study participants with recurrent urothelial carcinoma who received Keytruda had a median survival of 10.3 months compared with 7.3 months for those treated with chemotherapy. Although this difference may seem small, it represents a 30 percent reduction in the risk of death.

Urothelial carcinoma is a cancer of the lining of the bladder or other parts of the urinary tract. It is the most common type of bladder cancer, accounting for most of the 81,200 new cases expected to be diagnosed this year, according to the American Cancer Society.

Keytruda is a monoclonal antibody that blocks the PD-1 receptor, an immune checkpoint on T cells that plays a role in regulating immune function. Some tumors can hijack PD-1 to turn off immune responses against them, and drugs like Keytruda release the brakes and restore T-cell activity.

Keytruda is currently approved as first-line therapy for people with advanced or metastatic (spread to other parts of the body) urothelial carcinoma who are ineligible for platinum-based drugs such as cisplatin and as second-line treatment for those whose cancer did not respond to or relapsed after platinum-based chemotherapy.

Joaquim Bellmunt, MD, PhD, of the Dana-Farber Cancer Institute in Boston, presented two-year follow-up data from Merck's Phase III KEYNOTE-045 trial, which compared Keytruda versus chemotherapy for people with recurrent locally advanced or metastatic urothelial carcinoma of the bladder, ureters (tubes from the kidneys to the bladder), renal pelvis (part of the kidney that empties into the ureters) or urethra (a tube leading from the bladder out of the body).

The study included 542 people with cancer that had progressed during or after platinum-based chemotherapy. About three quarters were men, and the median age was 66. Most had metastasis to the lymph nodes, liver or other internal organs. The majority were starting their second therapy.

Participants were randomly assigned to receive either Keytruda by IV infusion every three weeks or the study investigator's choice of chemotherapy using docetaxel, paclitaxel or vinflunine.

Study enrollment started in November 2014 and the first analysis was done in September 2016, after the patients had been followed for a median of 14 months.

As reported in The New England Journal of Medicine, those results showed that the median overall survival was 10.3 months in the Keytruda group versus 7.4 months in the chemotherapy group. The difference was significant, meaning it was probably not due to chance. However, there was no significant difference in progression-free survival, meaning patients were still alive without worsening of disease. Side effects were less common in the Keytruda group compared with the chemotherapy group (61 percent versus 90 percent). The study was stopped ahead of schedule, but participants continued to be followed. About 60 percent of those originally assigned to chemotherapy received subsequent treatment, in some cases including immunotherapy.

At last week's conference, Bellmunt presented updated findings through October 2017, giving a median follow-up period of almost 28 months. At this point, no patients remained on treatment.

Overall survival rates at 12 months were 44.4 percent in the Keytruda group and 29.8 percent in the chemotherapy group; at 24 months, the rates were 27.0 percent and 14.3 percent, respectively. At 28 months, the median survival time was 10.3 months with Keytruda versus 7.3 months with chemotherapy, a significant difference. The risk of death was 30 percent lower in the Keytruda group.

Progression-free survival was slightly lower in the Keytruda group compared with the chemotherapy group (2.1 months versus 3.3 months), but the difference did not reach statistical significance, meaning it could have been attributable to chance.

However, response rates did favor immunotherapy. Overall response rates—meaning partial or complete tumor shrinkage—were 21.1 percent in the Keytruda group versus 11.0 percent in the chemotherapy group. Complete response rates were 9.3 percent and 2.9 percent, respectively. The median duration of response was 4.4 months in the chemotherapy group but was not reached in the Keytruda group because a majority of patients were still responding.

Overall survival was actually shorter for Keytruda recipients with higher levels of PD-L1 (the binding partner of PD-1) on their tumor cells and tumor-infiltrating immune cells—8.0 months versus 10.8 months for those with PD-L1 expression above and below 10 percent, respectively. Overall response rates were similar, 20.3 percent versus 19.9 percent, providing further evidence that PD-L1 expression is not a good predictor of treatment response. Those with higher PD-L1 levels did appear to have a longer duration of response, however.

Adverse events were more common in the chemotherapy group. Fatigue, nausea, loss of appetite, constipation, anemia, neutropenia and peripheral neuropathy were all substantially more likely with chemotherapy. More than 35 percent of chemotherapy recipients had hair loss compared with none of the Keytruda recipients. Itching and immune-related side effects such as hypothyroidism

and lung inflammation occurred more often in the Keytruda group.

Bellmunt concluded that these long-term results show that this immunotherapy was superior to chemotherapy in terms of overall survival and safety, providing Level 1 evidence—the most persuasive kind—for making Keytruda the standard of care for recurrent urothelial cancer.

Commenting on the findings, Robert Jones, MD, PhD, of the University of Glasgow concluded that checkpoint inhibitors like Keytruda have role for many patients with advanced urothelial cancer, but they are often ineffective. As seen in long-term melanoma results, it appears there may be a long “tail” with immunotherapy for bladder cancer, meaning a portion of responders will continue to respond indefinitely, but longer follow-up is needed, Jones said.

Click here to read the GU18 study abstract.

Click here to read the New England Journal of Medicine report about KEYNOTE-045.
