Keytruda Plus Inlyta Gets a New Indication for Kidney Cancer

Immunotherapy and targeted therapy combo is now approved for first-time treatment of advanced renal cell carcinoma.

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The Food and Drug Administration (FDA) has approved the checkpoint inhibitor Keytruda (pembrolizumab) in combination with the kinase inhibitor Inlyta (axitinib) for people with advanced renal cell carcinoma, the most common type of kidney cancer.

The approval—which came ahead of schedule—is for first-line treatment of patients with advanced RCC who have not previously received systemic therapy. Keytruda is administered as an IV infusion every three weeks and Inlyta is a pill taken twice daily.

This approval is supported by findings from the Phase III KEYNOTE-426 trial, which showed that Keytruda plus Inlyta delayed disease progression and reduced the risk of death by nearly half compared with standard therapy.

Nearly 74,000 people will be diagnosed with kidney cancer this year, according to the American Cancer Society. Renal cell carcinoma (RCC) accounts for more than 90% of these cases, and a majority of people with RCC have clear-cell cancer. Kidney cancer has few symptoms during its early stages, and many patients already have metastatic disease that has spread beyond the kidney by the time they are diagnosed. Standard treatment involves surgery followed by targeted therapy.

Keytruda, from Merck, is a monoclonal antibody that blocks the PD-1 receptor, an immune checkpoint on T cells that helps regulate immune function. Some tumors can hijack PD-1 to turn off immune responses against them. 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. Keytruda is already approved for several types of advanced cancer, most recently liver cancer. Checkpoint inhibitors don’t work for everyone; people with higher PD-L1 levels in their tumors tend to do better on this type of treatment, but this is not a reliable predictor of individual response.

Inlyta, from Pfizer, is a targeted therapy that blocks the VEGFR tyrosine kinase enzyme, which plays a role in cell growth and blood vessel development (angiogenesis). It is currently approved for second-line RCC therapy after trying other treatment. Drugs that interfere with angiogenesis

appear to promote infiltration of T cells into tumors, which could make checkpoint inhibitors like Keytruda work better, according to KEYNOTE-426 senior investigator Thomas Powles, MD, of Barts Cancer Institute in London.

Powles presented findings from KEYNOTE-426 at the 2019 Genitourinary

Cancers Symposium in February. The results were also recently published in the New England Journal of Medicine.

In this study, 861 participants with advanced clear cell RCC who had not received prior systemic therapy were randomly assigned to receive Keytruda plus Inlyta or the standard therapy Sutent (sunitinib), another oral tyrosine kinase inhibitor. Treatment continued until patients experienced disease progression or intolerable side effects.

Participants treated with Keytruda plus Inlyta saw an improvement in both progression-free survival (PFS)—meaning they were still alive without worsening of disease—and overall survival. The median PFS was 15.1 months in the Keytruda plus Inlyta group versus 11.1 months in the Sutent group. After a year on treatment, overall survival rates were 90% versus 78%, respectively—a 47% reduction in the risk of death. After 18 months, the corresponding rates were 82% and 72%.

Overall response rates, meaning complete or partial tumor shrinkage, were 59% with the Keytruda combination versus 36% with Sutent, including 6% and 2%, respectively, with complete tumor regression. Responses were seen regardless of progression risk (favorable, intermediate or poor) or PD-L1 expression level.

Treatment was generally safe, although side effects were common. Around 60% of people in both groups experienced severe (grade 3 or higher) treatment-related adverse events. However, treatment discontinuation because of side effects was uncommon. The most common side effects of Keytruda plus Inlyta include diarrhea, fatigue, weakness, hypertension, liver toxicity, hypothyroidism, decreased appetite, mouth sores, rash, voice changes (dysphonia) and hand-foot syndrome (palmar-plantar erythrodysesthesia), with redness, swelling and pain on the palms of the hands and soles of the feet.

Immune-mediated side effects are a concern with checkpoint inhibitors. Unleashing the immune system can lead to excessive immune responses that harm healthy organs. The Keytruda label includes a warning about immune-mediated inflammation of the lungs, colon, liver, kidneys, endocrine glands and skin. About 20% of study participants developed severe liver toxicity.

Bristol-Myers Squibb's checkpoint inhibitor Opdivo (nivolumab) is also approved for kidney cancer, but only for patients who received prior kinase inhibitors, or, in combination with Yervoy (ipilimumab), for previously untreated people with intermediate or poor progression risk.

"Given the aggressive nature of the disease, many patients with advanced renal cell carcinoma need additional treatment options that can help improve survival outcomes," Brian Rini, MD, of

Cleveland Clinic Cancer Center said in a Merck press release. “Pembrolizumab in combination with axitinib offers an important new therapeutic option for physicians to consider when approaching initial treatment for patients newly diagnosed with advanced renal cell carcinoma.”

Click here for updated prescribing information for Keytruda.

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