New Targeted Therapy Shows Promise for Kidney Cancer

MK-6482 shrank tumors in 24% of people with advanced renal cell carcinoma.

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An experimental targeted therapy that restricts blood vessel growth showed good activity against advanced renal cell carcinoma, the most common type of kidney cancer, according to a study presented at the American Society of Clinical Oncology Genitourinary Cancers Symposium last week in San Francisco.

“A new drug as a single agent showing an overall response rate of 24% across all risk categories—poor, intermediate and good and in a heavily refractory population—is quite promising,” presenter Toni Choueiri, MD, director of the Lank Center for Genitourinary Oncology at Dana-Farber Cancer Institute, said in a press release.

Renal cell carcinoma (RCC) accounts for more than 90% of kidney cancer. Among those with RCC, about 70% have clear-cell cancer, so called because of its appearance under a microscope. Kidney cancer has few symptoms during its early stages, and many people already have metastatic disease by the time they are diagnosed. Standard treatment typically involves surgery followed by targeted therapy that interferes with enzymes that play a role in cell growth and blood vessel development. Checkpoint inhibitor immunotherapy is also an option.

Choueiri and colleagues conducted a study of MK-6482 (formerly known as PT2977 before it was acquired by Merck), the first oral inhibitor of hypoxia-inducible factor-2-alpha, or HIF-2-alpha. This transcription factor plays a role in the body’s ability to sense oxygen levels and turn on genes to produce more red blood cells and form new blood vessels when oxygen is in short supply. Choueiri’s mentor, William Kaelin Jr., MD, of Dana-Farber, and others won the 2019 Nobel Prize in Physiology or Medicine for showing how this mechanism works.

Around 90% of people with kidney cancer have a defective tumor-suppressor protein called pVHL that leads to HIF-2-alpha activation, resulting in the proliferation of blood vessels that feed tumors. MK-6482 blocks HIF-2-alpha and shuts down blood vessel growth.

This Phase I/II study enrolled people with advanced solid tumors. After various doses of MK-6482 were tested, a cohort of 55 people with previously treated advanced clear-cell RCC were treated with the selected dose of 120 milligrams taken as a tablet once daily.

In this group, 80% were men, and the median age was 62. Ten were classified as having poor risk for disease progression, 40 had intermediate risk and five had favorable risk. All had received at least one prior systemic therapy, and a majority had tried three or more. Most (93%) had used VEGF inhibitors, and 73% had used checkpoint inhibitors; 67% had tried both.

After a median follow-up period of 13 months, the overall response rate, meaning complete or partial tumor remission, was 24%; all were partial responses. An additional 56% had stable disease. However, response rates varied by risk category: 40% for those with favorable risk, 25% for those with intermediate risk and 10% for those with poor risk.

By this point, 39 participants (71%) had stopped treatment, mostly due to disease progression, while 16 (29%) were still receiving MK-6482. Most patients (81%) experienced responses that lasted at least six months, and the median duration of response was not reached.

The median progression-free survival, meaning patients were still alive without worsening of their disease, was 11.0 months. This, too, varied by risk category: 16.5 months for those with favorable risk, 11.0 months for those with intermediate risk and 6.9 months for those with poor risk.

Treatment was generally safe, although side effects were common. Just over a third (36%) experienced severe (Grade 3 or higher) treatment-related adverse events. These included 14 people (26%) with severe anemia and eight (15%) with severe hypoxia, or low oxygen levels. Two people (4%) stopped treatment because of hypoxia. There were no deaths due to treatment-related adverse events.

The researchers concluded that MK-6482 showed “promising clinical activity” with a “favorable safety profile.”

A Phase III trial comparing MK-6482 against the mTOR inhibitor Afinitor (everolimus) in more than 700 people with previously treated advanced kidney cancer is currently underway and recruiting participants (ClinicalTrials.gov number NCT04195750).

Click here to read the study abstract.
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