Belzutifan induced strong responses in patients with von Hippel-Lindau disease-associated kidney cancer

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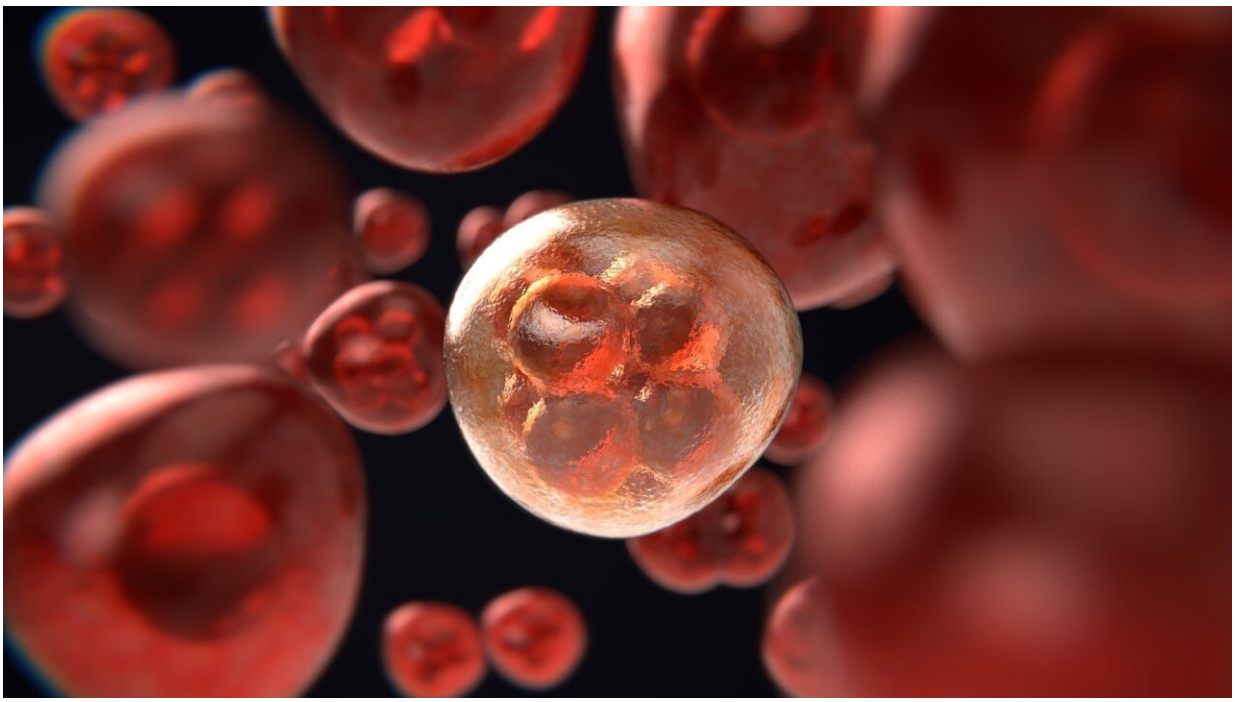

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Results from a Phase II trial led by researchers at The University of Texas MD Anderson Cancer Center showed that treatment with belzutifan, a small-molecule inhibitor of hypoxia-inducible factor (HIF)-2a, achieved strong clinical activity in patients with renal cell

carcinomas (RCC) and non-renal cell carcinoma neoplasms associated with von Hippel-Lindau (VHL) disease. The study was published today in the *New England Journal of Medicine.*

The objective response rate in patients with RCC was 49% after a median follow-up of 21.8 months. Additionally, 92% of patients had a decrease in the size of their target lesions. At 24 months, the percentage of patients with progression-free survival was 96%.

Belzutifan, originally known as MK-6482, was approved by the Food and Drug Administration on Aug. 13, 2021 based on previously reported results from this trial. It is the first FDA-approved therapy for VHL disease.

"Patients with von Hippel-Lindau disease are at risk of developing several types of cancer and require repeated surgical procedures to manage their tumors," said principal investigator Eric Jonasch, M.D., professor of Genitourinary Medical Oncology. "These results profoundly change the way we manage patients with VHL disease and will provide an impactful benefit to a majority of patients with VHL."

Treatment for VHL disease-associated cancers represents a significant unmet need

VHL disease is caused by a rare inherited mutation of the *VHL* gene and is associated with tumors forming in multiple organs. Some of these tumors are benign, but they can grow and cause damage to organs. VHL also can cause cancerous tumors in the kidney or pancreas. RCC affects approximately 40% of people with VHL disease and is one of the most common causes of disease-related death in these patients.

The *VHL* mutation causes cells to lose their ability to properly respond

to oxygen levels, leading to a buildup of HIF proteins. This process incorrectly signals that the cells are starved of oxygen, causing the formation of blood vessels and driving tumor growth. Inactivation of the VHL tumor-suppressor protein also is observed in more than 90% of sporadic RCC tumors. Belzutifan directly targets HIF-2a, hindering cancer cell growth, spread and abnormal blood vessel development.

Treatment of VHL disease-associated renal tumors consists of active surveillance until surgery is required for tumors larger than 3 cm to prevent metastatic disease. Repeated surgical procedures can carry significant complications, as many patients develop renal insufficiency. Surgery will not cure VHL disease in patients with RCC, but it is intended to prevent death from metastatic kidney cancer.

"Half of the patients in this trial had an objective response and almost all patients saw a decrease in the size of their lesions," Jonasch said. "Patients with VHL are able to have a better quality of life as this therapy can delay or avoid the need for surgery."

Trial suggests promising new treatment options for VHL-associated kidney cancer

The single-arm clinical trial enrolled 61 patients at 11 centers in the United States, Denmark, France and the United Kingdom. The study enrolled adult patients with a germline mutation diagnosis of VHL disease, no prior systemic cancer therapy, measurable non-metastatic RCC tumors and Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

Patients received belzutifan orally once daily until disease progression, unacceptable toxicity or decision to withdraw. Tumor size was evaluated at screening and every 12 weeks thereafter. No patients had progressive

disease on treatment and 54 patients (89%) remain on treatment.

Most treatment-related adverse events (AEs) were grade 1 or 2 in severity. The most common adverse events were anemia (90%) and fatigue (66%). No deaths occurred from a treatment-related adverse event.

Responses also were observed in 77% of patients with VHL-associated pancreatic lesions and 30% of patients with VHL-associated central nervous system hemangioblastomas. Among the 12 patients with retinal hemangioblastomas at baseline, 100% were graded as showing improvement.

"These data suggest HIF-2a inhibition offers an effective treatment option with manageable side effects for patients with VHL-associated renal cell carcinoma and other VHL-related tumors," Jonasch said. "I am excited to be able to provide this impactful therapy to patients who have waited a long time for new options."

The trial is limited by its lack of a control group and small sample size. Since there are no approved nonsurgical treatment options for VHL disease, designing a randomized controlled trial is an ethical challenge, Jonasch explained. Future studies may include testing whether this treatment can prevent the development of new lesions in patients with VHL disease.

More information: *New England Journal of Medicine* (2021). www.nejm.org/doi/full/10.1056/NEJMoa2103425

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