

Belzutifan outperforms everolimus in advanced kidney cancer treatment

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Belzutifan significantly reduced the risk of progression of clear cell renal cell carcinoma (ccRCC), the most common type of kidney cancer, in patients previously treated with immune checkpoint inhibitors and anti-angiogenic therapies compared with everolimus in a phase 3 clinical trial. The trial, led by Toni K. Choueiri, MD, Director of the Lank Center for Genitourinary Cancer at Dana-Farber Cancer Institute,

showed the risk of progression was reduced by 25-26%.

The results were presented at the annual European Society for Medical Oncology (ESMO) Congress on October 21, 2023, in Madrid, Spain.

"This is real progress for patients and could lead to approval of this drug for this patient group," says Choueiri, senior author on the presentation in Madrid.

Belzutifan, a HIF-2 α inhibitor, is currently approved for patients with Von Hippel-Landau (VHL) disease-associated [renal cell carcinoma](#), a form of kidney cancer. The drug was originally investigated and approved for kidney cancer patients with VHL disease because they have inherited a mutation that inactivates the *VHL* gene, which results in an overabundance of HIF-2 α in cells.

When overabundant in cells, HIF-2 α is associated with increased cancer-driving activity, such as cell proliferation, immune evasion, [low oxygen levels](#) (called hypoxia), and blood vessel formation (called angiogenesis). Dana-Farber's William G. Kaelin, Jr., MD, was awarded a [Nobel Prize in Physiology or Medicine in 2019](#) for the discovery of the role HIF-2 α in cancer and other diseases.

"The knowledge we have about hypoxia and angiogenesis in kidney [cancer](#) stemmed from this essential pre-clinical research at Dana-Farber," says Choueiri. "Bringing this knowledge forward to benefit patients is very gratifying."

While the mutation that causes VHL disease is inherited, spontaneous mutations that inactivate *VHL* occur in over 90% of ccRCC tumors, suggesting that a HIF-2 α inhibitor might also benefit patients with ccRCC.

This trial, called LITESPARK-005, enrolled 746 patients with metastatic ccRCC who had progressed after treatment with both an immune checkpoint inhibitor (ICI), such as a PD-1 or PD-L1 inhibitor, and an anti-angiogenic therapy. ICIs and anti-angiogenic medicines have become a standard part of first- and second-line therapies for metastatic ccRCC, though most patients eventually experience disease progression and need additional treatment options.

Patients were randomized to receive treatment with either belzutifan or everolimus. At the second interim analysis, after a median of 25.7 months, patients taking belzutifan were 26% less likely to have progressed compared with those taking everolimus.

The overall response rate was also higher with belzutifan, at 22% versus 3.5%, and 13 patients experienced a complete response with belzutifan compared to none with everolimus. Patients taking belzutifan were also less likely to discontinue therapy due to side effects.

"Importantly, quality of life favored belzutifan," says Choueiri.

There was an improvement in overall survival with belzutifan though it was not statistically significant.

This investigation of monotherapy with belzutifan is part of a broader strategy to learn more about the efficacy and safety of HIF-2 α inhibition in RCC. The strategy involves multiple LITESPARK trials examining belzutifan alone and in combination with other therapies in treatment-naive and pre-treated disease settings.

Choueiri also presented updated findings from the phase 2 LITESPARK-003 at the ESMO Congress that showed belzutifan plus cabozantinib showed durable antitumor activity and a safety profile consistent with prior observation [previously published](#) in *The Lancet*

Oncology.

More information: Belzutifan versus everolimus in participants (pts) with previously treated advanced clear cell renal cell carcinoma (ccRCC): randomized open-label phase 3 LITESPARK-005 study will be presented in Proffered Paper Session 2- Genitourinary tumors, non-prostate, October 21, 2023, European Society for Medical Oncology (ESMO) Congress

Provided by Dana-Farber Cancer Institute

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