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Clinical Trials Corner: The Challenge to Establish Optimal Treatment After Progression on Checkpoint Inhibitors

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Dear Readers,

The Clinical Trials Corner of *Kidney Cancer* highlights planned or ongoing high-impact studies in renal cell carcinoma (RCC). In this issue, we highlight the LITESPARK-011 trial, comparing the combination of lenvatinib plus belzutifan to cabozantinib in patients with refractory metastatic RCC.

In the future, if you feel that you would like to draw attention to a specific trial, please feel free to email us at mbparikh@ucdavis.edu or kca@iospress.com.

Sincerely,

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An Open-label, Randomized, Phase 3 Study of MK-6482 in Combination With Lenvatinib (MK-7902) vs. Cabozantinib in Participants with Advanced Renal Cell Carcinoma Who Have Progressed After Prior Anti-PD-1/L1 Therapy

Status: Recruiting

Clinicaltrials.gov identifier: NCT04586231

Sponsor: Merck Sharp & Dohme LLC in collaboration with Eisai Inc

Enrollment: 708

Rationale: While there are limited data that demonstrate efficacy of cabozantinib after treatment with checkpoint inhibitor therapy, optimal second line treatment after first-line anti-PD-1 therapy remains an area of active clinical interest. Belzutifan (MK-6482) is an inhibitor of hypoxia-inducible factor-2α (HIF-2α), which has established efficacy in patients with von Hippel-Lindau disease, but remains under clinical study in patients with clear cell RCC. HIF-2α also regulates vascular endothelial growth factor (VEGF) expression and is involved in resistance to anti-VEGF therapy. Thus, there is interest in combining belzutifan with a VEGF tyrosine kinase inhibitor (TKI) such as lenvatinib.

Study Design: This open label, Phase 3, multicenter study enrolls patients with unresectable, locally advanced or metastatic clear cell RCC. Patients must have experienced disease progression on or after an anti-PD-1/PD-L1 therapy as either first or second-line treatment in the advanced setting, or as adjuvant or neoadjuvant therapy with progression within 6 months of the last dose. Patients may not have received more than 2 prior systemic regimens, and could only have received 1 prior anti-PD/PD-L1 therapy. Patients also must have never received belzutifan, lenvatinib or cabozantinib prior to enrollment. Patients who are enrolled to the study receive either belzutifan + lenvatinib or cabozantinib until disease progression or unacceptable toxicity.

Endpoints: The co-primary endpoints of this study are progression-free survival (PFS) and overall survival (OS). Secondary endpoints include objective response rate (ORR), duration of response (DOR), and toxicity.

Comments: The optimal treatment after progression of current first-line therapies for mRCC is an emerging question. Recent studies such as CONTACT-03 evaluating the role of continuing immune checkpoint inhibition in combination with cabozantinib have not resulted in a benefit in PFS when compared to cabozantinib alone. Thus, combining a new treatment such as belzutifan, for which there is a preclinical rationale for possible synergistic activity with a VEGF TKI, with lenvatinib is of interest. This study was initiated in 2020, after which the landscape of first-line treatment for mRCC evolved. The Phase 3 CLEAR and CheckMate-9ER studies established the combinations of lenvatinib plus pembrolizumab and nivolumab plus cabozantinib as first line treatments. There remain eligible patients for this trial- patients with mRCC who receive nivolumab plus ipilimumab, pembrolizumab plus axitinib, or avelumab plus axitinib or patients who quickly develop mRCC after pembrolizumab treatment in the adjuvant setting. However, the clinical application of the results of this study may be limited given the shift the treatment landscape.

CONFLICT OF INTEREST

Mamta Parikh

Consultant: Bristol-Myers Squibb, Exelixis, Oncocyte, Natera, Pfizer, Seagen.