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Clinical Trials Corner: A Promising New Drug Class in Treating Metastatic Renal Cell Carcinoma

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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 first HIF-2α inhibitor to be studied in a Phase 3 clinical trial in patients with 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 Versus Everolimus in Participants With Advanced Renal Cell Carcinoma That Has Progressed After Prior PD-1/L1 and VEGF-Targeted Therapies

Status: Recruiting

Clinicaltrials.gov identifier: NCT04195750

Sponsor: Merck Sharp & Dohme Corp

Enrollment: 736

Rationale: While numerous advances have been made in the treatment of mRCC in the past decade, our armament has been limited to three classes of drugs- immunotherapy, vascular endothelial growth factor (VEGF) inhibitors, and inhibitors of the mammalian target of rapamycin (mTOR). While it has long been

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recognized that hypoxia inducible factor-2 (HIF-2) is a key transcription factor driving clear cell RCC, attempts to develop an inhibitor of this target in the past have been thwarted. Results from a Phase 1/2 study of the oral HIF-2α inhibitor, MK-6482, in patients with refractory mRCC, however, recently objective response rate (ORR) of 24% with a disease control rate of 80%. Of note, 67% of the patients on this study had received both antiangiogenesis agents as well as anti-PD-1 inhibitors. On the basis of these promising results, a Phase 3 study has been initiated.

Study Design: This Phase 3 randomized trial enrolls patients with locally advanced or metastatic clear cell RCC. Patients must have received systemic treatment in the advanced setting with a PD-1 or PD-L1 inhibitor and a VEGF targeted therapy, but must not have received more than 3 prior systemic regimens in this setting. Patients with significant cardiac disease are excluded from enrollment. Patients will be randomized to receive either MK-6482 or everolimus, both given once daily as oral therapies, until the time of disease progression or unacceptable toxicity.

Endpoints: The co-primary endpoints of this trial are progression-free survival (PFS) and overall survival (OS). Secondary endpoints include ORR, duration of response, safety and impact to quality of life.

Comments: This multi-center industry-sponsored, registrational trial is designed to assess the activity of the oral HIF-2α inhibitor, MK-6482, in patients with refractory advanced clear cell RCC. The study design does provide a few challenges which should be noted. The limitation of prior systemic regimens to 3 is potentially challenging, as patients who receive nivolumab and ipilimumab as their initial treatment may normally be treated with more than 2 subsequent anti-VEGF agents before resorting to everolimus. On the other hand, limiting prior regimens to 3 does allow for a more uniform patient population, as most patients will have received 2-3 prior anti-VEGF agents and 1 prior immune checkpoint inhibitor. Patients with HIV, Hepatitis B and Hepatitis C have also been excluded from this trial. Notable safety signals seen in the Phase 1/2 trial, of anemia, dyspnea, and hypoxia will be further interrogated with the study of MK-6482 in a larger patient population. The study is expected to accrue well based on the unmet need of new classes of drugs in treating mRCC and on the promising results from the Phase 1/2 trial.

CONFLICT OF INTEREST

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Consultant: Janssen, Exelexis