AN OPEN-LABEL PHASE 2 STUDY OF 2 DOSES OF THE HYPOXIA-INDUCIBLE FACTOR (HIF)-2α INHIBITOR BELZUTIFAN FOR THE TREATMENT OF ADVANCED CLEAR CELL RENAL CELL CARCINOMA AFTER PROGRESSION ON SYSTEMIC THERAPY

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Background Accumulation and aberrant stabilization of transcription factor HIF-2α drives the expression of genes associated with progression of clear cell renal cell carcinoma (ccRCC). Belzutifan, a first-in-class HIF-2α inhibitor, has demonstrated promising antitumor activity with a favorable safety profile in patients with heavily pretreated ccRCC. The efficacy and safety of 2 doses of belzutifan in patients with advanced ccRCC who experienced progression after systemic therapy will be evaluated in this randomized, open-label, multicenter, phase 2 trial (NCT04489771).

Methods Approximately 150 adults will be randomly assigned 1:1 to receive oral belzutifan 120 mg once daily or 200 mg once daily. Patients with locally advanced or metastatic ccRCC (per RECIST v1.1) who experienced progression on or after 1 line of anti-PD-1/PD-L1 therapy as monotherapy or combined with other agents, with the immediately preceding line of treatment an anti-PD-1/PD-L1 therapy and having demonstrated radiographic disease progression (per investigator). Other key eligibility criteria: ≤3 prior systemic regimens and a Karnofsky Performance Status Scale score ≥70%. Patients who previously received belzutifan or another HIF-2α inhibitor; require supplemental oxygen; have a baseline hemoglobin level <10 g/dL; have a history of HIV, hepatitis B, or hepatitis C infection; or have active central nervous system metastases are excluded. Patients will be stratified by International mRCC Database Consortium prognostic scores (0, 1 or 2, or 3–6) and by number of prior tyrosine kinase inhibitor–containing therapies (0, 1, 2 or 3). Treatment will continue until progression, unacceptable toxicity, or withdrawal of consent. Computed tomography or magnetic resonance imaging will be performed at baseline, every 8 weeks through week 49, and every 12 weeks thereafter. Adverse events will be monitored throughout the study and for 30 days after treatment (90 days for serious adverse events). The primary end point is objective response rate per RECIST v1.1 by blinded independent central review (BICR). Secondary end points are progression-free survival, duration of response, and clinical benefit rate per RECIST v1.1 by BICR, overall survival, pharmacokinetics, and safety. The study will enroll patients in at least 9 countries (Australia, Belgium, Greece, Ireland, Israel, Netherlands, Russia, the United Kingdom, and the United States) and is recruiting.

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Ethics Approval The study and the protocol were approved by the Institutional Review Board or ethics committee at each site.

Trial Registration ClinicalTrials.gov, NCT04489771

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