Treatment of Advanced Renal Cell Carcinoma After Progression on Systemic Therapy: Open-Label Phase 2 Study of 2 Doses of the HIF-2α Inhibitor Belzutifan

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Background
- Approximately 90% of clear cell renal cell carcinoma (ccRCC) is caused by a loss of function in the von Hippel-Lindau (VHL) gene, leading to the accumulation of hypoxia-inducible factor 2α (HIF-2α) and driving tumor growth in ccRCC (Figure 1). HIF-2α activates genes associated with invasion and metastasis, cell survival, resistance to the immune system, and angiogenesis.
- Treatment options for patients with advanced ccRCC are limited after immunotherapy and vascular endothelial growth factor (VEGF)-targeted therapy.
- Belzutifan (MK-6482) is a small molecule HIF-2α inhibitor that has shown antitumor activity in patients with advanced ccRCC after progression with other systemic therapies in a phase 1/2 study.
- Patients received belzutifan 120 mg orally once daily (QD); objective response rate (ORR) was 25%, and median progression-free survival (PFS) was 14.5 months.
- The median (range) number of prior systemic therapies was 3 (1-9); 34 patients (62%) had previously received ≥3 therapies.
- 44 patients (69%) had received anti-VEGF therapies before enrollment.
- 39 patients (71%) received a VEGF/VEGF receptor inhibitor and an immune checkpoint inhibitor.
- This randomized, open-label, phase 2 study (NCT04489771) was conducted to evaluate the efficacy and safety of 2 doses of belzutifan in patients with advanced ccRCC who experienced disease progression after systemic therapy.

Objectives
- Primary objectives are to identify molecular (genomic, metabolic, and/or proteomic) biomarkers that could be associated with clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of belzutifan.
- Secondary objectives include assessing the safety and tolerability of belzutifan for patients with advanced ccRCC, measuring other biomarkers that could be associated with clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of belzutifan.

Methods
- Study Design: Approximately 150 adults with advanced ccRCC that has progressed after a maximum of 3 prior systemic therapies will be enrolled in this randomized, open-label, multicenter, phase 2 study.
- Eligible patients will be randomly assigned 1:1 to receive belzutifan 120 mg or 200 mg QD; ~75 patients will be included in each dose arm.
- Study treatment will continue until documented disease progression, unacceptable toxicity, or withdrawal of the patient.

Patient Eligibility Criteria
- Key Inclusion Criteria
  - Age ≥18 years
  - Locally advanced/metastatic ccRCC (with or without sarcomatoid features)
  - Measurable disease per RECIST v1.1 by BICR
  - Disease progression after first-line systemic therapy with prior anti-PD-1/anti-PD-L1 + VEGF-targeted TKI combination
  - Radiographic disease progression after the most recent regimen (if >1 prior regimen)
  - Has not previously received ≥3 systemic therapies for locally advanced or metastatic ccRCC
  - KPS score ≥70% assessed within 10 days before first dose of study drug

- Key Exclusion Criteria
  - Known central nervous system metastases and/or carcinomatous meningitis
  - Prior treatment with belzutifan or another HIF-2α inhibitor or any type of small molecule kinase inhibitor ≤2 weeks before randomization
  - Received any systemic anticancer antibody ≤4 weeks before randomization
  - Active infection necessitating systemic therapy
  - History of HIV infection
  - History of hepatitis B virus infection or active hepatitis C virus infection

Assessments and Follow-Up
- Radiologic evaluation will occur at week 9, then Q8W for 49 weeks, and Q12W thereafter.
- Patients who experience progression or begin a new anticancer regimen will enter the survival follow-up phase.
- Adverse events (AEs) will be monitored throughout the study and graded in severity per Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.
- AEIs will be reported for 30 days after cessation of study drug.
- Serious AEIs will be reported for 90 days after cessation of study drug or for 30 days if the patient begins a new anticancer therapy regimen.

Status
- Patients will be enrolled in the study in at least 9 countries (Australia, Belgium, Greece, Ireland, Israel, Netherlands, Russia, the United Kingdom, and the United States); patients are being recruited (Figure 3).

Figure 1. The Role of Belzutifan in Inhibiting the HIF-2α Pathway

Figure 2. Study Design

Figure 3. Countries With Sites of Enrollment (green)

Key Eligibility Criteria
- Advanced or metastatic ccRCC
- Measurable disease per RECIST v1.1
- Disease progression after first-line systemic therapy
- Received ≥3 prior systemic therapies for advanced/metastatic ccRCC
- KPS score ≥70%

End Points
- Primary: ORR
- Secondary: PFS, OS, ORR, CBR, PK, and safety

Assessments
- Q8W after week 9 for the first 49 weeks and then Q12W thereafter

Key Inclusion Criteria
- Age ≥18 years
- Locally advanced/metastatic ccRCC (with or without sarcomatoid features)
- Measurable disease per RECIST v1.1 by BICR
- Disease progression after first-line systemic therapy with prior anti-PD-1/anti-PD-L1 + VEGF-targeted TKI combination
- Radiographic disease progression after the most recent regimen (if >1 prior regimen)
- Has not previously received ≥3 systemic therapies for locally advanced or metastatic ccRCC
- KPS score ≥70% assessed within 10 days before first dose of study drug

References

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