#TIP4

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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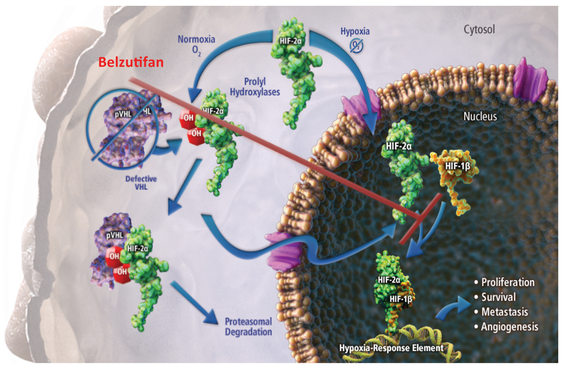
Background

- 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**)[1,2]
  - HIF-2α activates genes associated with invasion and metastasis, cell survival, resistance to the immune system, and angiogenesis[3]
  - 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[4]
  - 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 (80%) had received anti–PD-1 therapies and 50 patients (91%) 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

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



pVHL, von Hippel-Lindau tumor suppressor.

Objectives

Primary

- To compare the antitumor activity of the 120-mg QD dose and 200-mg QD dose of belzutifan for the treatment of patients with advanced ccRCC, measured by ORR per RECIST v1.1 by blinded independent central review (BICR)

Secondary

- To compare the following between the 120-mg QD and 200-mg QD doses of belzutifan for the treatment of patients with advanced ccRCC
  - PFS per RECIST v1.1 by BICR
  - Duration of response (DOR) per RECIST v1.1 by BICR
  - Clinical benefit rate (CBR), defined as the percentage of patients who achieve complete response, partial response, or stable disease of ≥6 months, evaluated per RECIST v1.1 by BICR
  - Overall survival (OS)
  - Safety and tolerability
  - Pharmacokinetics (PK)

Exploratory

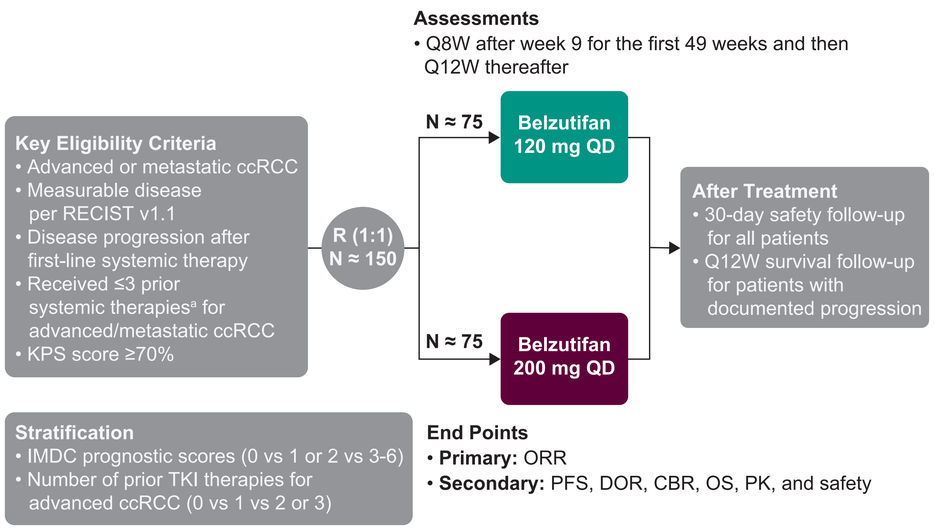
- To identify molecular (genomic, metabolic, and/or proteomic) biomarkers that could be associated with clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of belzutifan

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 (**Figure 2**)
  - Prior systemic therapy must include a first-line anti–PD-1/anti–PD-L1 + cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) or anti–PD-1/anti–PD-L1 + VEGF-targeted tyrosine kinase inhibitor (TKI) combination
- Eligible patients will be randomly assigned 1:1 to receive belzutifan 120 mg or 200 mg QD; ~75 patients will be included in each treatment arm
  - At randomization, patients will be stratified by International mRCC Database Consortium (IMDC) prognostic scores (0 vs 1 or 2 vs 3-6) and by number of prior TKI therapies for advanced ccRCC (0 vs 1 vs 2 or 3)
- Study treatment will continue until documented disease progression, unacceptable toxicity, or withdrawal of the patient

Figure 2. Study Design



KPS, Karnofsky Performance Status Scale; Q8W, every 8 weeks; Q12W, every 12 weeks; R, randomization.

[a]Prior systemic therapies must include first-line anti–PD-1/anti–PD-L1 + anti–CTLA-4 or anti–PD-1/anti–PD-L1 + VEGF-targeted TKI combination.

Patient Eligibility Criteria

Key Inclusion Criteria	Key Exclusion 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 + anti–CTLA-4 combination or 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	• 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, in which they will be followed up for survival status approximately Q12W after the treatment discontinuation visit or discontinuation of follow-up imaging
- Adverse events (AEs) will be monitored throughout the study and graded in severity per Common Terminology Criteria for Adverse Events (CTCAE), version 5.0
  - AEs will be reported for 30 days after cessation of study drug
  - Serious AEs will be reported for 90 days after cessation of study drug or for 30 days if the patient begins a new anticancer therapy regimen
- A posttreatment safety follow-up visit will occur 30 days after the last dose of study drug is administered

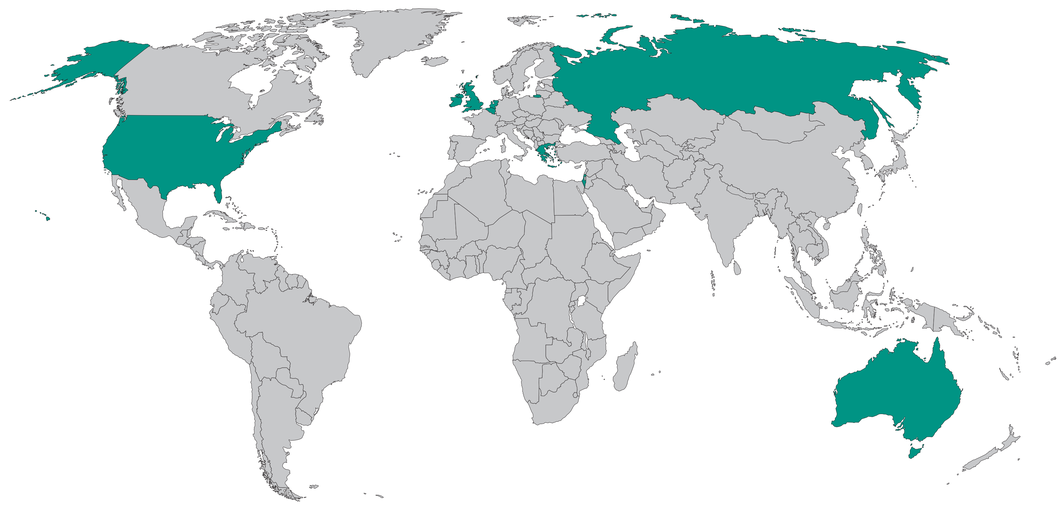
Analysis

- The efficacy analysis will be performed for the intention-to-treat population (all randomly assigned patients)
  - The primary end point ORR will be evaluated using the stratified Miettinen and Nurminen method,[5] with strata weighted by sample size
  - The secondary end points PFS and OS will be summarized within each treatment group using the Kaplan-Meier method; the hazard ratio will be estimated using a stratified Cox regression model
- The safety analysis will be performed for the all-patients-as-treated population (all randomly assigned patients who received ≥1 dose of study drug)
  - For analyses in which 95% CIs will be provided for between-treatment differences in the percentage of participants who experience events, the Miettinen and Nurminen method will be used

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 3. Countries With Sites of Enrollment (green)



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