Randomized, Open-Label, Phase 3 Study of Belzutifan Plus Lenvatinib Versus Cabozantinib in Patients With Advanced Renal Cell Carcinoma After Anti–PD-1/PD-L1 Therapy

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Background
- There is no standard of care for patients with advanced clear cell renal cell carcinoma (ccRCC) that has progressed after use of PD-1/PD-L1 inhibitors or vascular endothelial growth factor (VEGF)-targeted therapies
- Approximately 90% of ccRCCs result in the loss of function of the von Hippel-Lindau (VHL) tumor suppressor gene, leading to the accumulation of hypoxia-inducible factor 2α (HIF-2α) and promoting tumor growth (Figure 1)1
  - HIF-2α induces genes associated with angiogenesis, invasion, metastasis, resistance to the immune system, and the cell survival mechanism2
- Belzutifan (MK-6482) is a small molecule HIF-2α inhibitor that has shown antitumor activity in a phase 1b study in patients with advanced ccRCC that has progressed after other systemic therapies
  - Patients received belzutifan 120 mg orally once daily; objective response rate (ORR) was 25%, and median progression-free survival (PFS) was 14.5 months1
- Among the genes activated by HIF-2α is VEGFA3, the VEGF/VEGFR pathway is commonly targeted by approved therapies, such as the tyrosine kinase inhibitors cabozantinib4 and lenvatinib,5 for management of advanced ccRCC
- This open-label, multicenter, randomized, active-controlled, phase 3 study (NCT04586231) is being conducted to compare the efficacy and safety of belzutifan + lenvatinib with that of cabozantinib alone in patients with advanced ccRCC who experienced disease progression on or after anti–PD-1/PD-L1 therapy

Objectives
Primary
- To compare the following for belzutifan + lenvatinib versus cabozantinib for the treatment of patients with advanced ccRCC who have experienced progression on or after anti–PD-1/PD-L1 therapy
  - PFS per RECIST v1.1 by blinded independent central review (BICR)
  - Overall survival (OS)
Secondary
- To compare the following for belzutifan + lenvatinib versus cabozantinib for the treatment of patients with advanced ccRCC who have experienced progression after anti–PD-1/PD-L1 therapy
  - ORR and duration of response (DOR) per RECIST v1.1 by BICR
  - Safety and tolerability

Methods
Study Design
- Approximately 708 adults with advanced ccRCC who experienced disease progression on or after first- or second-line systemic treatment with anti–PD-1/PD-L1 monotherapy or in combination with another agent for locally advanced or metastatic ccRCC will be enrolled (Figure 2)
  - The immediately preceding line of treatment must be an anti–PD-1/PD-L1 therapy, with no more than 2 prior systemic regimens and only 1 prior anti–PD-1/PD-L1 therapy for locally advanced or metastatic RCC allowed
  - Eligible patients will be randomly assigned 1:1 to receive either belzutifan 120 mg orally + lenvatinib 20 mg orally once daily (QD) or cabozantinib 60 mg orally QD: 354 participants will be included in each treatment arm
  - At randomization, patients will be stratified based on International mRCC Database Consortium (IMDC) prognostic scores (0 vs 1 or 2 vs 3-6), number of prior lines of therapy (1 vs 2), and geographic region (North America, Western Europe, or rest of world [ROW])
- Study treatment will continue until documented disease progression, start of a new anticancer treatment, unacceptable toxicity, or withdrawal of the patient

Figure 2. Study Design

Key Eligibility Criteria
- Advanced or metastatic RCC with clear cell component
- Disease progression after first- or second-line anti–PD-1/PD-L1 therapy
  - Immediately preceding therapy must be anti–PD-1/PD-L1
  - Received ≤2 prior systemic therapies
  - Measurable disease per RECIST v1.1
  - KPS score ≥70%
- Stratification
  - IMDC prognostic scores (0 vs 1 or 2 vs 3-6)
  - Number of prior lines of therapy (1 vs 2)
  - Geographic region (North America vs Western Europe vs ROW)

Assessments
- QBW for the first 80 weeks and then Q12W thereafter

Patient Eligibility Criteria

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<thead>
<tr>
<th>Key Inclusion Criteria</th>
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<tr>
<td>Age ≥18 years</td>
<td>Central nervous system metastases and/or carcinomatous meningitis</td>
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<td>Locally advanced or metastatic ccRCC (with or without sarcomatoid features)</td>
<td>Moderate to severe hepatic impairment (Child-Pugh classification B or C)</td>
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<td>Measurable disease per RECIST v1.1 as assessed by the local site investigator/radiology</td>
<td>Prior treatment with belzutifan or another HIF-2a inhibitor, lenvatinib, or cabozantinib</td>
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<td>Disease progression on or after first- or second-line systemic therapy with anti–PD-1/PD-L1 agents for locally advanced or metastatic ccRCC</td>
<td>Receipt of any type of small molecule kinase inhibitor ≤2 weeks before randomization</td>
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<td>The immediately preceding therapy must be anti–PD-1/PD-L1</td>
<td>Receipt of any systemic cancer antibody ≤4 weeks before randomization</td>
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<td>Previously received no more than 2 systemic therapies and no more than 1 anti–PD-1/PD-L1 therapy for locally advanced or metastatic ccRCC</td>
<td>Active infection necessitating systemic therapy</td>
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<td>KPS score ≥70% assessed within 10 days before randomization</td>
<td>History of HIV infection</td>
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<td>History of hepatitis B virus or active hepatitis C virus infection</td>
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Figure 3. Countries With Sites of Enrollment (green)

References

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