Investigational Immune and Targeted Combination Therapies for Patients With Advanced Clear Cell Renal Cell Carcinoma: A Phase 1b/2 Umbrella Study

Background
- Novel combination therapies with improved antitumor activity can be identified through umbrella platform studies, which allow for rapid, concurrent, and efficient testing of multiple investigational agents in sub-studies of patients who require new treatment options.
- This umbrella platform study is an open-label, rolling-arm, multicenter, phase Ib/2 with an adaptive design, a safety lead-in phase, and an efficacy phase that will be conducted to evaluate the safety and efficacy of experimental combinations of investigational agents with different mechanisms of action in advanced clear cell renal cell carcinoma (ccRCC).
  - Cytotoxic T-lymphocyte–associated protein 4 (CTLA-4; quavonlimab [MK-1308])
  - Hypoxia-inducible factor 2α (HIF-2α; belzutifan [MK-6482])
  - Lymphocyte activation gene 3 (LAG-3; MK-4280)
  - Immunoglobulin-like transcript 4 (ILT4; MK-4433)
  - PD-1 (pembrolizumab)
  - Vascular endothelial growth factor (VEGF)–tyrosine kinase inhibitor (TKI) (lenvatinib).
- Sub-study 03A (NCT04026479) will be conducted to evaluate treatment combinations in previously untreated patients, and sub-study 03B (NCT04626518) will be conducted to evaluate patients whose disease progresses on PD-1/PD-L1 inhibitors and VEGF-TKIs.
  - Given the promising efficacy results in the RCC cohort of the phase 1b KEYNOTE-146 trial (NCT0250196) and the recent phase 3 CLEAR study (NCT02811861), pembrolizumab in combination with lenvatinib will be used as the reference arm in sub-study 03A and sub-study 03B.

Methods

Study Design
- Figure 1. Study Design for Sub-study 03A

Patient Eligibility Criteria

<table>
<thead>
<tr>
<th>Key Inclusion Criteria</th>
<th>Both Studies</th>
<th>Key Exclusion Criteria</th>
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<tr>
<td>Age ≥18 years</td>
<td>Radiotherapy within 2 weeks or major surgery within 3 weeks of start of treatment</td>
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<td>Histologically confirmed locally advanced or metastatic ccRCC (with or without sarcomatoid features)</td>
<td>Current pneumothorax, history of interstitial lung disease, or history of (noninfectious) pneumonitis necessitating use of steroids</td>
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<td>Measurable disease per RECIST v1.1 as assessed by BICR</td>
<td>Clinically significant cardiac disease</td>
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<td>KPS score ≥70%</td>
<td>No prior systemic therapy for advanced ccRCC (03A only)</td>
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<tr>
<td>Tissue for biomarker analysis</td>
<td>No substudy-specific exclusion criteria</td>
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Assessment and Follow-Up

- Objective response rate (ORR) of each treatment arm per RECIST v1.1 as assessed by blinded independent central review (BICR)
- Safety and tolerability of each treatment arm (proportion of patients who experienced adverse events [AEs])
- Safety and tolerability will be assessed by clinical review and summarized using descriptive statistics (ie, counts and percentages)
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Analysis

- Safety analysis population comprises all randomly assigned patients who received ≥1 dose of study treatment
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