First-Line MK-1308A + Lenvatinib or Pembrolizumab + Belzutifan + Lenvatinib Versus Pembrolizumab + Lenvatinib for Clear Cell Renal Cell Carcinoma: A Randomized, Open-Label, Phase 3 Study

Background
- Despite advances in treatment, most patients with advanced clear cell renal cell carcinoma (ccRCC) will eventually experience disease progression on treatment1-5.
- Combination therapy with the PD-1 inhibitor pembrolizumab + the vascular endothelial growth factor receptor (VEGFR)-tyrosine kinase inhibitor (TKI) lenvatinib demonstrated superior progression-free survival (PFS), overall survival (OS), and objective response rate (ORR) versus sunitinib and is approved as first-line treatment for RCC2.
- The current study is designed to evaluate whether the addition of an anti–cytotoxic T-lymphocyte–associated protein 4 (CTLA-4; quavonlimab) or a hypoxia-inducible factor 2α (HIF-2α) inhibitor (belzutifan) can improve patient outcomes when added to pembrolizumab + lenvatinib.
- In this open-label, multicenter, randomized, active-controlled, phase 3 study (NCT04736706), the efficacy and safety of MK-1308A (coformulation of quavonlimab + pembrolizumab) + lenvatinib and of belzutifan + pembrolizumab + lenvatinib will be compared with that of pembrolizumab + lenvatinib in treatment-naive patients with advanced ccRCC.

Objectives
- To compare the efficacy and safety of MK-1308A + lenvatinib and that of belzutifan + pembrolizumab + lenvatinib with the efficacy and safety of pembrolizumab + lenvatinib.

Dual Primary End Points
- PFS per RECIST v1.1 by blinded independent central review (BICR).
- OS.

Secondary End Points
- ORR and duration of response (DOR) per RECIST v1.1 by BICR.
- Safety and tolerability.

Methods

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>Known additional malignancy that is progressing or necessitated treatment within the past 3 years</td>
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<td>Locally advanced or metastatic ccRCC with or without sarcomatoid features</td>
<td>Central nervous system metastases and/or carcinomatous meningitis</td>
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<td>Measurable disease per RECIST v1.1 as assessed by the local site investigator/radiology</td>
<td>Radiotherapy ≤2 weeks before first dose of study intervention</td>
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<tr>
<td>No prior systemic therapy for advanced ccRCC</td>
<td>Hypoxia, defined as pulse oximeter reading &lt;92% at rest, or supplemental oxygen (intermittent or long-term)</td>
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<tr>
<td>KPS score ≥70%</td>
<td>Clinically significant cardiac disease ≤12 months before first dose of study treatment</td>
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Key Eligibility Criteria
- Advanced or metastatic ccRCC
- No prior systemic therapy
- Measurable disease per RECIST v1.1
- KPS score ≥70%

Stratification
- IMDC prognostic scores (0 vs 1 or 2 vs 3-6)
- Geographic region (North America vs Western Europe vs ROW)

End Points
- Primary: PFS per RECIST v1.1 by BICR, OS.
- Secondary: ORR per RECIST v1.1 by BICR, DOR per RECIST v1.1 by BICR, safety, and tolerability.

Assessment and Follow-Up

Triplet: CTLA-4/PD-1/TKI MK-1308A, (Quavonlimab 25 mg + Pembrolizumab 400 mg) IV Q6W + Lenvatinib 20 mg PO QD

Treatment
- Pembrolizumab and MK-1308A treatment will be limited to 18 infusions (~2 years).
- Treatment will be continued until disease progression or discontinuation event.

Assessments
- Tumor imaging at week 12, then Q4W up to week 78, and then Q12W thereafter.
- Additional safety follow-up contact (visit or phone contact) will be conducted 60 and 90 days after the date of discontinuation of study drug.
- Safety results will be analyzed following a tiered approach.
- The Miettinen and Nurminen method, with strata weighted by sample size.
- The efficacy analysis population consists of all randomly assigned patients (intention to treat).
- PFS and OS will be evaluated using a stratified log-rank test.
- The hazard ratio will be estimated using stratified Cox proportional hazards models, and event rates over time will be estimated within each treatment group using the Kaplan-Meier method.

Analyses

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References

Status
- The study is enrolling or planning to enroll at sites in Africa, Asia, Australia, Europe, North America, and South America.

Figure 2. Countries With Sites of Enrollment (green)

Contact Information
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