#TIP2

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

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Background

- Despite advances in treatment, most patients with advanced clear cell renal cell carcinoma (ccRCC) will eventually experience disease progression on treatment[1-5]
- 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 RCC[2]
- 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

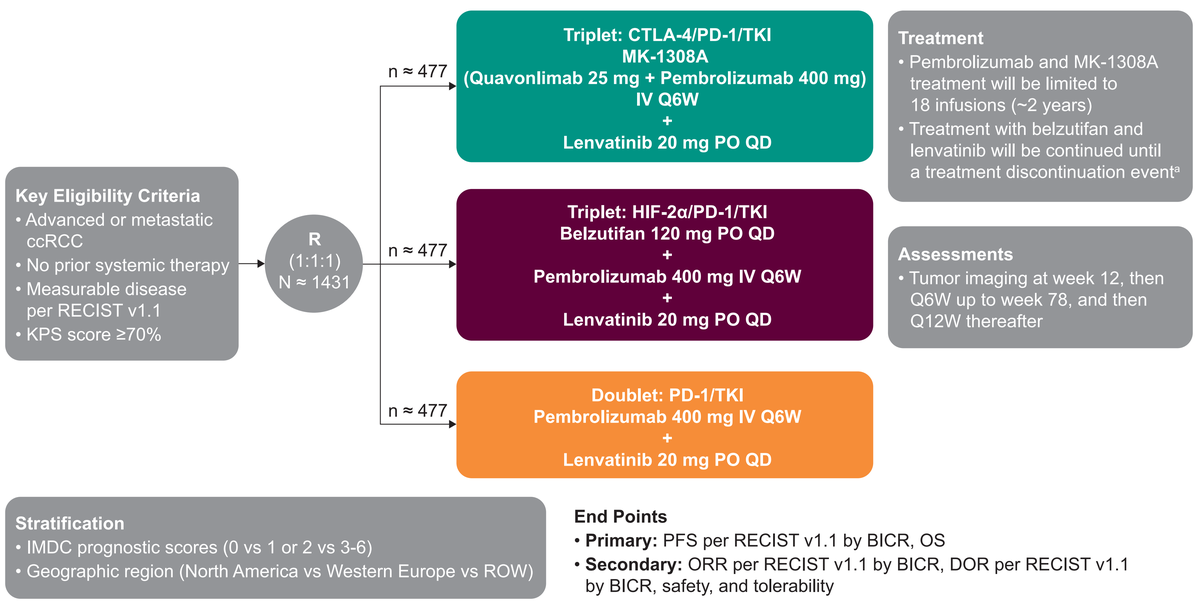
Methods

Patient Eligibility Criteria

Key Inclusion Criteria	Key Exclusion Criteria
• Age ≥18 years • Locally advanced or metastatic ccRCC (with or without sarcomatoid features) • Measurable disease per RECIST v1.1 as assessed by the local site investigator/ radiology • No prior systemic therapy for advanced ccRCC • KPS score ≥70%	• Known additional malignancy that is progressing or necessitated treatment within the past 3 years • Central nervous system metastases and/or carcinomatous meningitis • Radiotherapy ≤2 weeks before first dose of study intervention • Hypoxia, defined as pulse oximeter reading <92% at rest, or supplemental oxygen (intermittent or long-term) • Clinically significant cardiac disease ≤12 months before first dose of study treatment

KPS, Karnofsky Performance Status Scale.

Figure 1. Study Design



IMDC, International mRCC Database Consortium; IV, intravenously; PO, by mouth; Q6W, every 6 weeks; Q12W, every 12 weeks; QD, once daily; R, randomization; ROW, rest of world.
[a]Documented disease progression, start of a new anticancer treatment, unacceptable toxicity, or withdrawal of the patient.

Assessment and Follow-Up

Assessment	Details
AEs	• AEs will be monitored throughout the study and for 90 days after cessation of study treatment • AEs will be graded per the guidelines outlined in CTCAE v5.0
Tumor response	• Tumor imaging (computed tomography or magnetic resonance imaging) as assessed per RECIST v1.1 by BICR will be performed at 12 weeks from the date of random assignment, Q6W until week 78, or more frequently if clinically indicated • After 78 weeks, patients who remain on treatment will undergo imaging Q12W • If positive bone imaging at baseline, subsequent bone imaging will be done at week 18, then Q12W through week 78, and then Q24W until disease progression is verified by BICR • After randomization, brain imaging will be performed as clinically indicated and to confirm complete response in patients with brain metastases at baseline
After treatment	• Posttreatment safety follow-up visit will occur within 30 days after discontinuation of study treatment • Additional safety follow-up contact (visit or phone contact) will be conducted 60 and 90 days after the date of discontinuation of study drug

AE, adverse event; CTCAE v5.0, Common Terminology Criteria for Adverse Events, version 5.0; Q24W, every 24 weeks.

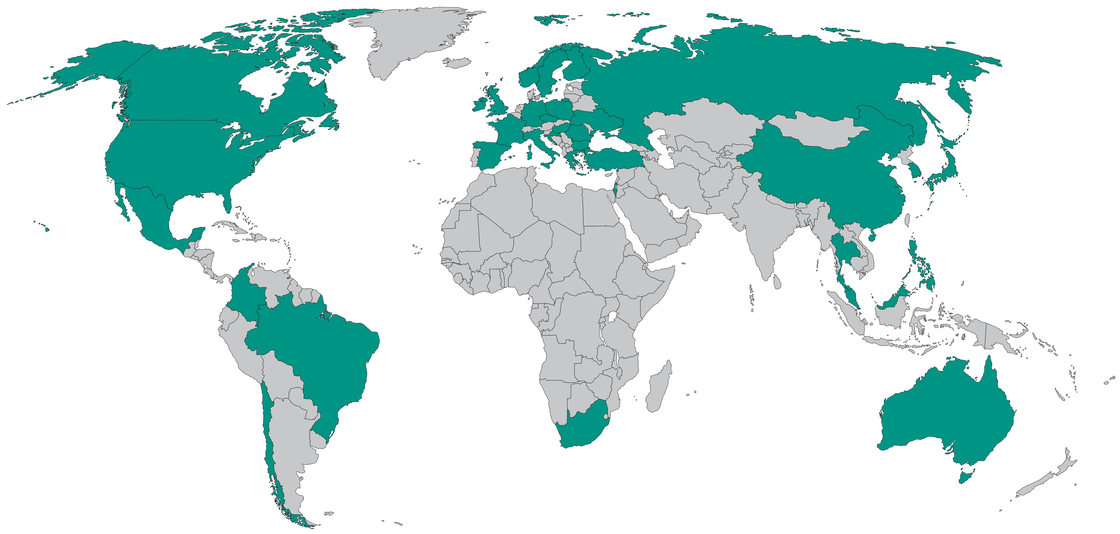
Analyses

Analyses	Details
Efficacy	• 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 • ORR will be analyzed using the stratified Miettinen and Nurminen method,[6] with strata weighted by sample size
Safety	• The safety analysis population consists of all randomly assigned patients who received ≥1 dose of study treatment (all patients as treated) • Safety results will be analyzed following a tiered approach • The Miettinen and Nurminen[6] method will be used to perform analyses in which 95% CIs will be provided for between-treatment differences in the percentages of patients who experienced events

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)



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