#TIP7

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

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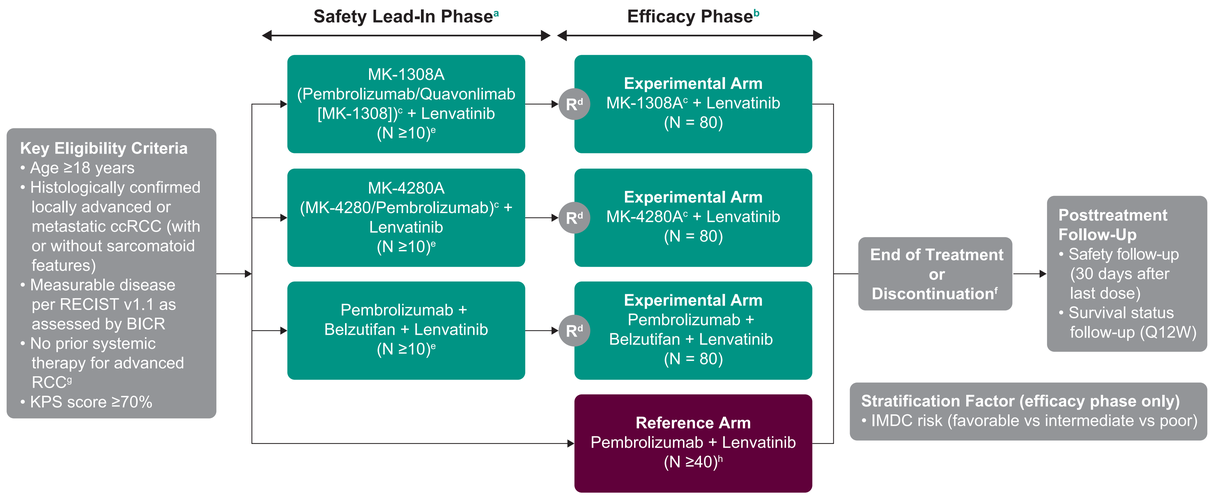
Background

- 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 substudies of patients who require new treatment options
- This umbrella platform study is an open-label, rolling-arm, multicenter, phase 1b/2 trial 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-4830)
  - PD-1 (pembrolizumab)
  - Vascular endothelial growth factor (VEGF)–tyrosine kinase inhibitor (TKI) (lenvatinib)
- Substudy 03A (NCT04626479) will be conducted to evaluate treatment combinations in previously untreated patients, and substudy 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/2 KEYNOTE-146 trial (NCT02501096) and the recent phase 3 CLEAR study (NCT02811861),[1,2] pembrolizumab in combination with lenvatinib will be used as the reference arm in substudy 03A and substudy 03B

Methods

Study Design

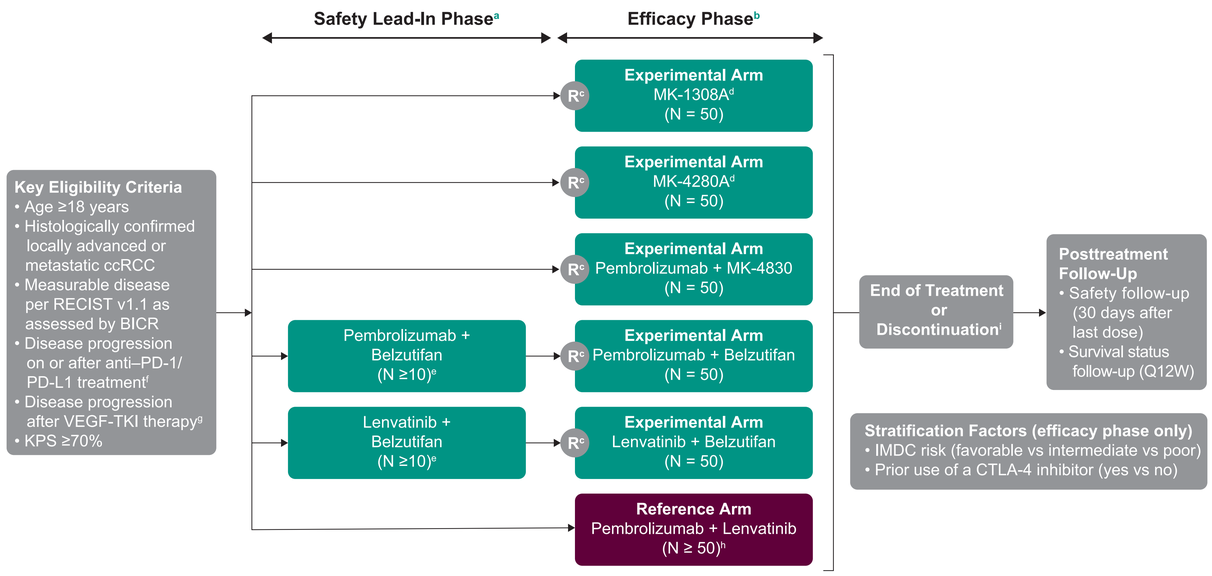
Figure 1. Study Design for Substudy 03A



IMDC, International mRCC Database Consortium; KPS, Karnofsky Performance Status scale; Q12W, every 12 weeks; R, randomization.

[a]A safety lead-in phase is necessary for experimental combinations with investigational agents without an established RP2D, if applicable.
[b]Patients will enter the efficacy phase if the treatment combinations demonstrate a tolerable safety profile outside this study or via the safety lead-in phase of this study.
[c]Fixed-dose coformulation.
[d]For each new experimental combination cohort entering the efficacy phase, patients will be randomly assigned 2:1 to receive the new experimental combination or the reference treatment (pembrolizumab + lenvatinib).
[e]The exact N value for experimental arms in the safety lead-in phase will depend on the number of doses assessed. Patients in this phase are not randomly assigned.
[f]Treatment will continue until radiographic disease progression, unacceptable toxicity, intercurrent illness that prevents further administration of study treatment, or withdrawal of consent.
[g]Neoadjuvant or adjuvant therapy is acceptable if completed ≥12 months before randomization.
[h]The patients in the reference arm can be shared if more than 1 experimental arm is open for enrollment. Therefore, additional patients will be enrolled in the reference arm with each new experimental arm to ensure a ratio of 2:1.

Figure 2. Study Design for Substudy 03B



[a]A safety lead-in phase is required for experimental combinations with investigational agents without an established RP2D, if applicable.
[b]Patients will enter the efficacy phase if the treatment combinations demonstrate a tolerable safety profile outside this study or via the safety lead-in phase of the study.
[c]For each new experimental combination arm, patients will be randomly assigned 1:1 to receive the new experimental combination or the reference treatment (pembrolizumab + lenvatinib).
[d]Fixed-dose coformulation.
[e]The exact N value for experimental arms in the safety lead-in phase will depend on the number of doses assessed. Patients in this phase are not randomly allocated.
[f]In sequence or in combination with a VEGF-TKI.
[g]In sequence or in combination with a PD-1/PD-L1 inhibitor.
[h]The patients in the reference arm can be shared if more than 1 experimental arm is open for enrollment. Therefore, additional patients will be enrolled in the reference arm with each new experimental arm to ensure a ratio of 1:1.
[i]Treatment will continue until radiographic disease progression, unacceptable toxicity, intercurrent illness that prevents further administration of study treatment, or withdrawal of consent.

Objectives

Primary Objectives

- To assess the following in patients with advanced ccRCC:
  - Safety lead-in phase
    - Safety and tolerability and the recommended phase 2 dose (RP2D), if applicable, of treatment combinations that have not been evaluated in separate studies
  - Efficacy phase
    - Safety and tolerability of each treatment arm (proportion of patients who experienced adverse events [AEs])
    - Objective response rate (ORR) of each treatment arm per RECIST v1.1 as assessed by blinded independent central review (BICR)

Secondary Objectives

- To assess the following in patients with advanced ccRCC:
  - Efficacy phase
  - Duration of response (DOR) per RECIST v1.1 as assessed by BICR
  - Progression-free survival (PFS) per RECIST v1.1 as assessed by BICR
  - Overall survival (OS)
  - Clinical benefit rate (CBR [complete response (CR) + partial response (PR) + stable disease ≥6 months]) per RECIST v1.1 as assessed by BICR

Patient Eligibility Criteria

Key Inclusion Criteria	Key Exclusion Criteria
Both Studies	
• Age ≥18 years • Histologically confirmed locally advanced or metastatic ccRCC (with or without sarcomatoid features) • Measurable disease per RECIST v1.1 as assessed by BICR • KPS score ≥70% • Tissue for biomarker analysis	• Radiotherapy within 2 weeks or major surgery within 3 weeks of start of treatment • Current pneumonitis, history of interstitial lung disease, or history of (noninfectious) pneumonitis necessitating use of steroids • Clinically significant cardiac disease
Study 03A	
• No prior systemic therapy for advanced ccRCC (03A only) – Prior neoadjuvant or adjuvant therapy for RCC ≥12 months before random assignment is allowed	• No substudy-specific exclusion criteria
Study 03B	
• Disease progression (RECIST v1.1) on or after systemic treatment for locally advanced or metastatic RCC with a VEGF-TKI therapy in sequence or in combination with a PD-1/PD-L1 inhibitor; if a PD-1/PD-L1 inhibitor is the first therapy, the patient must have received ≥2 doses (03B only)	• More than 4 prior systemic anticancer therapies (03B only) • Prior therapy with pembrolizumab + lenvatinib, belzutifan, or another HIF-2α inhibitor (03B only)

Assessment and Follow-Up

Assessment	Details
AEs	• AEs will be monitored throughout the study and for 30 days after cessation of study treatment (90 days for serious AEs) and will be graded per the guidelines outlined in the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0
RP2D	• For experimental arms for which there is a safety lead-in phase, DLTs observed in the first 21 days of study treatment in up to 10 DLT-evaluable patients per dose level will be used to determine the preliminary RP2D based on the modified toxicity probability interval design
Tumor response	• Tumor imaging (computed tomography or magnetic resonance imaging and bone imaging) as assessed by BICR per RECIST v1.1 will occur at 12 weeks (03A) or 6 weeks (03B) from the date of random assignment, every 6 weeks until week 54, or more frequently if clinically indicated • After 54 weeks, patients who remain on treatment will undergo imaging Q12W

DLT, dose-limiting toxicity.

Analyses

Analyses	Details
Safety	• The safety analysis population comprises all randomly assigned patients who received ≥1 dose of study treatment • Safety and tolerability will be assessed by clinical review and summarized using descriptive statistics (ie, counts and percentages)
Efficacy	• The efficacy analysis population will include all randomly assigned patients in the efficacy phase (intention to treat) – Efficacy analysis in the safety lead-in phase will be conducted on all treated patients • ORR and CBR estimates will be reported with 90% and 95% CIs, respectively, using the Clopper-Pearson method • PFS and OS will be estimated using the nonparametric Kaplan-Meier method • DOR will be summarized descriptively using the Kaplan-Meier method if sample size permits; only patients with confirmed CR or PR will be included in the analysis of DOR

Status

- Substudy 03A is enrolling at 15 sites in Australia, Canada, Israel, New Zealand, Spain, South Korea, and the United States
- Substudy 03B is enrolling at 27 sites in Australia, Israel, New Zealand, South Korea, Spain, and the United States

References

1. Lee C-H et al. *J Clin Oncol.* 2020;38(suppl 15). Abstract 5008.
2. Motzer R et al. *N Engl J Med.* 2021;384:1289-1300.

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