PHASE 3 STUDY OF PEMBROLIZUMAB + BELZUTIFAN + LENVATINIB OR PEMBROLIZUMAB/QUAVONLIMAB + LENVATINIB VERSUS PEMBROLIZUMAB + LENVATINIB AS FIRST-LINE TREATMENT FOR ADVANCED RENAL CELL CARCINOMA

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Background Pembrolizumab + vascular endothelial growth factor (VEGF) inhibitor lenvatinib demonstrated antitumor activity as first-line treatment for advanced clear cell renal cell carcinoma (ccRCC) in phase 3 trial KEYNOTE-581/CLEAR (NCT02811861). Hypoxia-inducible factor 2 α (HIF-2 α) inhibitor belzutifan (MK-6482) showed antitumor activity in ccRCC, and a coformulation of pembrolizumab and CTLA-4 inhibitor quavonlimab (MK-1308A) showed antitumor activity in non-small cell lung cancer. HIF-2 α or CTLA-4 inhibition with PD-1 and VEGF inhibition backbone combination may provide additional benefit as first-line treatment in ccRCC. This open-label, randomized, phase 3 study (NCT04736706) will be conducted to compare novel combination therapies pembrolizumab + belzutifan + lenvatinib (arm A) and MK-1308A + lenvatinib (arm B) with pembrolizumab + lenvatinib (arm C).

Methods Approximately 1431 adults with metastatic ccRCC, measurable disease per RECIST v1.1, and Karnofsky Performance Status Scale score $\geq 70\%$ who had not previously undergone systemic therapy for advanced ccRCC will be enrolled. Patients will be randomly assigned 1:1:1 to arm A (belzutifan 120 mg + lenvatinib 20 mg oral once daily + pembrolizumab 400 mg IV every 6 weeks), arm B (MK-1308A [quavonlimab 25 mg + pembrolizumab 400 mg] IV every 6 weeks and lenvatinib 20 mg oral once daily), or arm C (pembrolizumab 400 mg IV every 6 weeks + lenvatinib 20 mg oral once daily). Treatment will continue until documented disease progression, withdrawal of consent, or other discontinuation event; patients will receive pembrolizumab and MK-1308A for up to 18 cycles (approximately 2 years). Patients will be stratified by International mRCC Database Consortium (IMDC) score (favorable vs intermediate vs poor), region of the world (North America vs Western Europe vs rest of the world), and sarcomatoid features (yes vs no). Response will be assessed by CT or MRI per RECIST v1.1 by blinded independent central review (BICR) at week 12 from randomization, every 6 weeks through week 78, and every 12 weeks thereafter. Adverse events and serious adverse events will be monitored throughout the study and for 90 days after treatment. Dual primary end points are progression-free survival per RECIST v1.1 by BICR and overall survival. Primary end points will be assessed in arm A compared with arm C and in arm B compared with arm C for patients with IMDC intermediate/poor status and in all patients regardless of IMDC status. Secondary end points are objective response rate and duration of response per RECIST v1.1 by BICR, patient-reported outcomes, and safety.

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Trial Registration ClinicalTrials.gov, NCT04736706

Ethics Approval The study and the protocol were approved by the Institutional Review Board or ethics committee at each site.

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