

Clinical Trials Corner

The Importance of Ipilimumab?

Dear Readers,

The Clinical Trials Corner of *Kidney Cancer* highlights planned or ongoing high-impact studies in renal cell carcinoma (RCC). In this issue, we discuss a Phase 3b trial with important practical implications in the treatment of RCC.

In the future, if you feel that you would like to draw attention to a specific trial, please feel free to email us at mbparikh@ucdavis.edu or kca@iospress.com.

Sincerely,

Mamta Parikh, MD, MS
Associate Editor, *Kidney Cancer*
Assistant Professor, University of California Davis School of Medicine
Department of Internal Medicine
Division of Hematology Oncology
Sacramento, California

A Phase 3b, Randomized, Double-blind Study of Nivolumab Combined with Ipilimumab Versus Nivolumab Monotherapy for Patients With Previously Untreated Advanced Renal Cell Carcinoma and Intermediate- or Poor-Risk Factors

Status: Recruiting

Clinicaltrials.gov identifier: NCT03873402

Sponsor: Bristol-Myers Squibb

Enrollment: 418

Rationale: The CheckMate-025 trial, evaluating nivolumab versus everolimus in patients with metastatic RCC progressed after antiangiogenesis therapy, established an overall survival benefit with the use of nivolumab; the objective response rate (ORR) for nivolumab in that trial was 25%. Subsequently the combination of nivolumab and ipilimumab was compared to sunitinib in the CheckMate-214 trial in patients with newly diagnosed metastatic RCC with intermediate- to poor-risk disease by International Metastatic RCC Database Consortium (IMDC) criteria; the study demonstrated a median overall survival advantage with nivolumab plus ipilimumab compared to sunitinib (not reached versus 26.0 months; hazard ratio (HR)= 0.63; $p < 0.001$). The ORR for the combination was 42%. The combination of nivolumab plus ipilimumab led to 46% Grade 3 and higher adverse events (AEs); 35% of patients in the nivolumab plus ipilimumab group required treatment with high-dose glucorticoids due to immune-related AEs. Pembrolizumab was also studied as monotherapy, in patients with previously untreated advanced RCC, in the KEYNOTE-427 trial. In this single arm study, the ORR was 33.6%. Nivolumab has not been studied in the first-line setting, and increased toxicity is observed with the combination of nivolumab plus ipilimumab, driving the design of this trial.

Study Design: This Phase 3b study enrolls patients with newly diagnosed advanced or metastatic RCC, who have not previously received any systemic therapy for RCC, who have histologically confirmed predominantly clear cell subtype RCC; patients with clear cell disease with sarcomatoid features are also included. Patients

must have intermediate or poor risk disease based on the International Metastatic RCC Database Consortium (IMDC) criteria. They cannot have received any immune checkpoint or T-cell co-stimulation therapy. Patients will be randomized to receive, in a double-blinded manner, either nivolumab and ipilimumab or nivolumab and placebo.

Endpoints: The primary endpoint of the trial is progression-free survival (PFS) and ORR. Secondary endpoints include overall survival, disease control rate (DCR), duration of response (DOR), time to objective response (TTR), as well as AEs.

Comments: This multi-center international trial asks an important question regarding the role of intensification of immune checkpoint inhibition in the treatment of intermediate- and poor-risk advanced RCC. While treatment of advanced RCC now involves several options for dual therapy, including nivolumab plus ipilimumab and pembrolizumab plus axitinib, both of which have demonstrated improvement in overall survival in comparison to sunitinib, these combination approaches come with increased toxicity that can be discouraging to the patient as well as the practicing oncologist. While the KEYNOTE-427 trial (Cohort A) did show an impressive ORR of ~34%, this was a single-arm trial. This randomized, double blind trial has the potential to address the true benefit of combination immune checkpoint inhibition versus anti-PD-1 therapy alone, as well as to better assess the true toxicity of the combination versus nivolumab alone. Ultimately, this study could provide oncologists the option to treat with anti-PD-1 therapy alone in the first-line setting in intermediate- and poor-risk patients, though the study will require some time to mature in order to evaluate the results meaningfully.