Kidney Cancer 3 (2019) 197–198
DOI 10.3233/KCA-199002
IOS Press

Clinical Trials Corner

When should we incorporate TKIs?

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 novel Phase 3 trial evaluating the optimal timing for incorporation of cabozantinib after initial treatment with immune checkpoint inhibitor therapy for patients with metastatic 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

PD-Inhibitor (Nivolumab) and Ipilimumab Followed by Nivolumab vs. VEGF TKI Cabozantinib With Nivolumab: A Phase III Trial in Metastatic Untreated Renal Cell Cancer [PDIGREE]

Status: Recruiting

Clinicaltrials.gov identifier: NCT03793166

Sponsor: National Cancer Institute (NCI)

Enrollment: 1046

Rationale: Based on the results of the CheckMate-214 trial, an overall survival (OS) advantage has been observed in patients with newly diagnosed metastatic RCC with intermediate- to poor-risk disease by International Metastatic RCC Database Consortium (IMDC) criteria when treated with nivolumab and ipilimumab as compared to sunitinib (OS not reached versus 26.0 months; hazard ratio (HR)= 0.63; $p<0.001$). The objective response rate (ORR) for the combination was 42%. Patients receiving nivolumab and ipilimumab receive 4 treatments with ipilimumab, after which, as long as there is no evidence of progressive disease (PD), they continue to receive nivolumab. Both the JAVELIN Renal 101 and KEYNOTE 426 trials demonstrated an advantage to combining a checkpoint inhibitor with axitinib as compared to treatment with sunitinib alone in Phase 3 trials, with some suggestion that ORR was higher with these combinations. An ongoing Phase 3 trial (CheckMate 9ER) is evaluating the combination of nivolumab plus cabozantinib versus sunitinib in patients with mRCC. It is unclear, after combination immune checkpoint inhibition, whether the combination of immune checkpoint inhibitor therapy and TKI is of benefit.

Study Design: This Phase 3 study enrolls patients with newly diagnosed IMDC intermediate or poor risk 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

ISSN 2468-4562/19/$35.00

features are also included. Patients will be randomized to two arms. In both arms, patients will be treated with induction immune checkpoint inhibitor therapy, involving nivolumab and ipilimumab every 21 days. In Arm A, after induction therapy, if there is evidence of PD, patients will be treated with cabozantinib continuously; all other patients will continue on nivolumab treatment every 28 days until progression or unacceptable toxicity. In Arm B, after induction therapy, patients who have PD will be treated cabozanitinib until further progression or toxicity. Patients who achieve a complete response (CR) will remain on nivolumab alone. Patients who are found to have a partial response or stable disease will receive a combination of nivolumab with cabozantinib until progression or unacceptable toxicity.

Endpoints: The primary endpoint of the trial is OS. The secondary endpoints include progression-free survival (PFS), CR at 12 months, ORR, and proportion of patients discontinuing protocol-directed treatment prior to 1 year. Incidence of adverse events will also be reported.

Comments: This multi-center trial brings us closer to understanding the role of combination of immune checkpoint inhibitor with TKI therapy. Ideally, a trial comparing dual immune checkpoint inhibition (nivolumab plus ipilimumab) to a checkpoint inhibitor with TKI (ie pembrolizumab plus axitinib) would help us to answer the question of optimal sequencing of therapy. However, such a trial would require large numbers of patients as well as extended follow-up, thus is likely not feasible in the short-term. As such, we currently have the option to treat patients with IMDC intermediate or poor risk mRCC with either nivolumab plus ipilimumab or a checkpoint inhibitor in combination with axitinib. For patients who are treated with nivolumab plus ipilimumab, this study will demonstrate the utility of incorporating cabozantinib in combination with checkpoint inhibitor before the time of overt progression. This will shed further light into the potential synergism of TKIs and immune checkpoint inhibitor, and may help guide sequencing therapy moving forward.