

Clinical Trials Corner: Optimizing Papillary Renal Cell Carcinoma Care

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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 highlight the PAMMET-2 study, an important Phase II study evaluating the treatment of patients with advanced papillary renal cell carcinoma (pRCC).

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,

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A Phase II Randomized Trial of Cabozantinib (NSC#761968) With or Without Atezolizumab (NSC#783608) in Patients with Advanced Papillary Renal Cell Carcinoma (PAMMET2)

Status: Recruiting

Clinicaltrials.gov identifier: NCT05411081

Sponsor: National Cancer Institute

Enrollment: 200

Rationale: The Phase II PAMMET was a landmark study in that it was the first randomized trial assessing targeted therapies in patients with papillary renal cell carcinoma (pRCC), a rare histologic subtype observed in 15% of patients with RCC. In the study, cabozantinib was found to have a longer progression free survival (PFS) compared with sunitinib in patients with metastatic pRCC. Since the initiation of that trial, immune checkpoint inhibitors (ICIs) have become a vital foundation of first-line treatment of advanced clear cell RCC, and some trials of ICI combinations have included a non-clear cell RCC cohort, a heterogeneous population. Thus, SWOG has initiated a clinical trial evaluating a vascular endothelial growth factor tyrosine kinase inhibitor (VEGF TKI) cabozantinib with or without a checkpoint inhibitor in this specific patient population.

Study Design: This study enrolls patients with metastatic histologically confirmed pRCC (either Type 1 or Type 2) with radiographically measurable disease who are ICI- and cabozantinib-naïve and who have been treated with one or fewer targeted therapies for pRCC. Following enrollment, patients are randomized to receive either 60 mg of cabozantinib orally or 60 mg of cabozantinib orally plus atezolizumab 1200 mg intravenously every 3 weeks, until the time of disease progression or unacceptable toxicity.

Endpoints: The primary endpoint of this trial is progression-free survival (PFS). Key secondary outcomes include overall survival (OS), objective response rate (ORR), and quantitative & qualitative adverse events observed in each treatment arm.

Comments: Treatment for metastatic clear cell RCC has evolved over the last decade, incorporating ICI therapy, often in combination with a VEGF TKI. Since non-clear cell RCC is less common, studying patients with these histologic subtypes has been more challenging. The Phase II PAPMET study was a landmark trial that impressively enrolled patients with metastatic pRCC and demonstrated a superior PFS with cabozantinib compared to sunitinib. However, many of the combinations that have established activity in clear cell RCC have trials enrolling non-clear cell RCC. PAPMET2 will thus face some increased challenges with accrual, especially as a Phase II study of nivolumab combined with cabozantinib enrolled mostly pRCC patients and established activity of this combination. As such, PAPMET2 having an arm that does not include an ICI may give some investigators pause. Similarly, the choice of atezolizumab may also cause hesitation, as this ICI has not demonstrated superior OS in combination with VEGF TKIs as of yet in clear cell RCC. Another interesting aspect of this trial is the choice of dose of cabozantinib, as trials combining nivolumab with cabozantinib have treated patients with 40 mg of cabozantinib daily; in this study, the dose will be 60 mg in both arms. Thus, tolerance of this dose level in combination with ICI will be an important observation. The strength of this study is its uniformity in enrolling patients with pRCC, which is important as retrospective studies have reflected heterogeneity in outcomes based on histologic subtypes undoubtedly in part due to differences in responses to currently available therapies.

CONFLICT OF INTEREST

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Consultant: AstraZeneca, Janssen, Exelixis, Seagen, Oncocyte, Signatera