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Clinical Trials Corner

Innovative Approaches to Immune Checkpoint Inhibition in Kidney Cancer

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 Phase 2 trials evaluating histologic subtypes with poor prognoses and underrepresentation in clinical trials- namely, patients with Xp11.2 translocations and those with collecting duct carcinoma.

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 Randomized Phase 2 Trial of Axitinib/Nivolumab Combination Therapy vs Single Agent Axitinib or Nivolumab for the Treatment of TFE/Translocation Renal Cell Carcinoma (tRCC) Across All Age Groups

Status: Recruiting
Clinicaltrials.gov identifier: NCT03595124
Sponsor: National Cancer Institute (NCI)

Enrollment: 87

Rationale: Translocation Renal Cell Carcinomas (tRCC), characterized by Xp11.2 translocation or TFE3 gene fusions, represent a rare subset of metastatic RCC with a poor prognosis. Patients tend to present at a younger age, and while rare in adults, tRCC represent about half of all pediatric RCCs. Historically, patients with this RCC subtype have highly aggressive disease, which tends to be refractory to typical RCC therapies. However, there are no formal treatment recommendations for this disease, and previously, no prospective trials had been conducted to study this subtype.

Study Design: This phase 2, randomized, multicenter, open-label trial (ECOG AREN1721) is enrolling patients with histologically confirmed unresectable or metastatic tRCC of patients age >1 years, as long as Body Surface Area is >0.53 m^2. Patients may not have received VEGF-targeted therapies or anti-PD-1 or anti-PD-L1 antibodies, but other therapies are allowed. Patients will be randomized to 1 of 3 arms, receiving either axitinib and nivolumab (Arm A), axitinib alone (Arm B), or nivolumab alone (Arm C). Patients will be treated to progression or until 2 years if there is disease control. A total of 4 years of follow-up is planned.

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Endpoints: The primary endpoint of the trial is PFS. Antitumor immune response and stability of T cell activation will be studied in an exploratory fashion. The study will also study the clinical behavior for up to 4 years of translocation morphology renal cell carcinoma.

Comments: This study is the first prospective trial studying patients with tRCC, and will require awareness and participation from all oncologists treating genitourinary malignancies to successfully accrue. While the study will undoubtedly include a large pediatric cohort, adult patients also need to be studied to see if clinical behavior and response to therapies are similar. The study may help to better elucidate the pathophysiology of this particular subtype to better explain its aggressive behavior. It may also contribute to our understanding of response or lack of response to targeted and immune checkpoint therapies for this patient population.

Prospective Phase II Study of Gemcitabine Plus Platinum Salt in Combination with Bevacizumab (Avastin) for Metastatic Collecting Duct Carcinoma

Status: Recruiting
Clinicaltrials.gov identifier: NCT02363751
Sponsor: UNICANCER

Enrollment: 41

Rationale: Though there is increasing awareness of the heterogeneity of RCC, collecting duct carcinoma has long been recognized as a separate entity, amounting to <1% of all kidney cancers. This subtype has been noted because of its aggressive behavior, and low likelihood of responding to conventional RCC regimens. Platinum-based chemotherapy has typically been used, extrapolating largely from treatment of urothelial carcinoma. As such, and on the basis of a preceding Phase I trial, a Phase II trial is evaluating the combination of gemcitabine, platinum agent, and bevacizumab in patients with metastatic collecting duct carcinoma.

Study Design: This is a phase 2 open label European multi-site study enrolling patients with metastatic collecting duct or medullary carcinoma which is histologically confirmed, who are treatment naïve in the metastatic setting, $\geq$ 18 years of age, and with adequate end organ function. Once enrolled, patients receive gemcitabine plus a platinum salt plus bevacizumab. If patients achieve disease control on this regimen, with either stable disease or a partial or complete response, then treatment is continued with bevacizumab monotherapy until progression.

Endpoints: The primary outcome of the trial is a composite endpoint of objective response rate (RR) and progression-free survival (PFS) rate at 6 months. Secondary endpoints include PFS, overall survival (OS), and toxicity.

Comments: This study is noteworthy in that collecting duct kidney cancer is rare, aggressive and has only been studied in a limited manner in clinical trials. Typically these patients are excluded from trials evaluating regimens for mRCC, or are enrolled in too small numbers to derive any conclusions. Given the similarities collecting duct kidney cancer shares histopathologically with urothelial carcinoma, the use of platinum-based chemotherapy is rational. On the other hand, the study is permitting enrollment of patients with medullary RCC. Though this subtype has some overlapping features with collecting duct kidney cancer, it is a distinct entity. For example, while it does also confer a poor prognosis with an aggressive phenotype, medullary RCC occurs more frequently in patients with sickle cell disease and is characterized by loss of INI1 expression. Thus, there could be some potential confounding with enrollment of both subtypes into this trial. Nevertheless, it is commendable to evaluate this rare subset of patients with platinum-based chemotherapy. Immune checkpoint inhibitors, having now demonstrated efficacy in both urothelial and renal cell carcinomas, are being studied in patients with non-clear cell RCC as a broad category, which will also provide additional information about new potential approaches towards these aggressive subtypes.