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Clinical Trials Corner: Is the Era of Theranostics Imminent?

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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 an earlier stage trial than usual, but one we should monitor with enthusiasm given the incorporation of the novel approach of targeted peptide receptor radionuclide therapy.

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 1b/2 Study of Combination ^{177}Lu Girentuximab Plus Cabozantinib and Nivolumab in Treatment naïve Patients with Advanced Clear Cell RCC

Status: Recruiting

Clinicaltrials.gov identifier: NCT05663710

Sponsor: M.D. Anderson Cancer Center

Enrollment: 100

Rationale: Girentuximab, a monoclonal antibody that targets carbonic anhydrase IX (CAIX), an enzyme highly expressed in clear cell RCC, has been evaluated in a radiolabeled fashion in localized RCC. A Phase 3 ZIRCON study of ^{89}Zr-DFO-girentuximab (TLX250-CDx) showed that TLX250-CDx was well tolerated and could accurately and noninvasively identify clear cell RCC. Extrapolating the trajectory of the advent of PSMA PET imaging followed by ^{177}LuPSMA treatment options for patients with metastatic prostate cancer, it is provocative to consider the possibility of a similar theranostic approach to improve the effect of current front-line treatments in metastatic RCC. This is especially compelling if, by conjugating radioisotopes to receptor binding analogs targeting CAIX, a radioligand treatment could activate the immune microenvironment to lead to a greater complete response (CR) rate.

Study Design: This open label, Phase 1b/2 single-center study enrolls patients with locally advanced or metastatic predominantly clear cell RCC, with at least one measurable lesion as defined by RECIST v1.1. Patients with ECOG performance status of 0-1 with adequate hematologic and organ function who have not previously received any frontline systemic therapy for metastatic RCC will be enrolled. All patients enrolled to treatment will undergo a pre-treatment PET scan and biopsy. Patients will be treated with ^{177}Lu-girentixuimab every 12 weeks for up to 3 treatments. After the first cycle (12 weeks) of treatment, nivolumab and cabozantinib will be added. The first five patients will be enrolled for the purposes of safety lead-in to evaluate myelosuppression. Patients will be treated for a maximum of 3 treatments of ^{177}Lu-girentuximab and will continue on nivolumab plus cabozantinib until progression or unacceptable toxicity.

Endpoints: The co-primary endpoints of this study are to determine safety of the combination of ^{177}Lu-girentuximab with nivolumab plus cabozantinib and to evaluate the CR rate with the combination in patients with previously untreated clear cell RCC. Secondary objectives include objective response rate (ORR) and progression free survival (PFS) of the combination. The study will also evaluate the effects of the combination on inducing activated T cell infiltration as exploratory endpoints.

Comments: As mentioned, the Phase 3 ZIRCON study did demonstrate the utility of radiolabeled girentuximab to characterize localized clear cell RCC. In the metastatic setting, diagnostic imaging studies are still ongoing and are certainly not the standard of care. Interestingly, in this pilot study evaluating the use of ^{177}Lu-girentuximab as a treatment, [18F]F-AraG radiotracer is used for PET imaging rather than TLX250-CDx, perhaps owing to availability. This may be prescient as, if this treatment does demonstrate efficacy, subsequent trials would be more pragmatic if a conventional PET would be sufficient to monitor for treatment. While this study is truly signal-finding, the study should also inform further the role of radiation-induced DNA damage on the effects of immune checkpoint inhibitor therapy in metastatic RCC, as this modality allows for targeted radiation to cancer cells throughout the body.

CONFLICT OF INTEREST

Mamta Parikh

Consultant: Bristol-Myers Squibb, Exelixis, Oncocyte, Natera, Pfizer, Seagen.