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Clinical Trials Corner: Reimagining RADICAL

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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 revisit the RADICAL trial, an important study evaluating the potential benefit of Radium-223 therapy in RCC patients with bone metastases, which has recently been amended.

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 Radium-223 Dichloride and Cabozantinib in Patients with Advanced Renal Cell Carcinoma with Bone Metastasis (RADICAL).

Status: Recruiting

Clinicaltrials.gov identifier: NCT04071223

Sponsor: Alliance for Clinical Trials in Oncology/National Cancer Institute

Enrollment: 210

Rationale: Roughly a third of patients with metastatic RCC have bone metastases, with the prevalence higher in patients with intermediate or poor risk disease. This leads to increased morbidity in these patients due to skeletal related events (SREs), and data suggest that these patients also have decreased survival. In the Phase III METEOR trial, cabozantinib appeared to particularly benefit the subset of patients with bone metastases compared to everolimus, both in terms of clinical endpoints as well as in changes in bone turnover markers. Radium-223, an alpha emitting radioisotope and calcium-mimetic, has been shown to decrease SREs in patients with metastatic castration resistant prostate cancer. An exploratory Phase I trial of Radium-223 combined with either sorafenib or pazopanib in patients with mRCC with at least one bone metastasis demonstrated

significant declines in bone turnover markers. Given these findings suggesting combination activity of tyrosine kinase inhibitors with Radium-223, and the evidence suggesting benefit of cabozantinib in patients with bone involvement, this Phase II study evaluates whether there is benefit to addition of Radium-223 to cabozantinib.

Study Design: This Phase II randomized trial enrolls patients with advanced RCC of any histologic subtype with at least 1 metastatic bone lesion that has not been previously irradiated. Patients may have had any number of prior lines of systemic therapy, but cannot have previously received cabozantinib. Prior Radium-223 dichloride treatment is also an exclusion criteria. Patients will be randomized to receive either Radium-223 dichloride every 28 days with cabozantinib 40 mg every day, or cabozantinib 40 mg every day. Patients in the combination arm will be treated with 6 treatments of Radium-223 dichloride and cabozantinib until disease progression or unacceptable toxicity; patients in the cabozantinib arm will be treated until disease progression or unacceptable toxicity.

Endpoints: The primary endpoint of this trial is symptomatic skeletal event (SSE)-free survival of the combination of Radium-223 and cabozantinib compared to cabozantinib alone. Secondary endpoints include SSE-free survival in predefined subgroups, progression free survival (PFS), overall survival (OS), time to first SSE, toxicity and objective response rate (ORR). The effect on markers of bone turnover will be examined as a correlative endpoint.

Comments: This cooperative group sponsored multi-center Phase II trial evaluates RCC patients with bone metastases, a population with poor outcomes both in terms of morbidity and mortality. Importantly, while Radium-223 dichloride has been studied alone in patients with prostate cancer and in combination with antiangiogenesis agents in patients with mRCC, this study will better evaluate whether there is a benefit to Radium-223 added to treatment. Prior studies did not have a control arm, and this study has a cabozantinib-alone comparator arm. With correlative analysis of markers of bone turnover in this study, there is potential to further understanding of the mechanism of the effect of both Radium-223 dichloride and cabozantinib on osseous metastases. Importantly, the study chairs have recently updated the eligibility criteria as outlined in the Study Design, allowing now for patients who only have one untreated bony lesion and for patients who are asymptomatic from osseous metastases. The trial eligibility requirements have also been adjusted to allow for a hemoglobin threshold of > 9. These changes should encourage readers to consider this important trial when evaluating a patient with progressive osseous metastases. The challenge in this trial, of course, is that data from trials like METEOR have led to an increased use of cabozantinib early in the treatment of mRCC patients with bony metastases, and may lead some to even use first-line nivolumab plus cabozantinib on the basis of the CheckMate-9ER study. However, it is important to note that these studies stratified for osseous metastases, in contrast to the RADICAL study, which specifically studies mRCC patients with a preponderance of bony metastases.

CONFLICT OF INTEREST

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