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Clinical Trials Corner: Raising the SABR to Renal Cell Carcinoma

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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 SAMURAI trial, evaluating the role of stereotactic ablative radiation therapy (SABR) in 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,

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Randomized Phase II Stereotactic Ablative Radiation Therapy (SABR) for Metastatic Untreated Renal Cell Carcinoma (RCC) Receiving Immunotherapy (SAMURAI)

Status: Recruiting

Clinicaltrials.gov identifier: NCT05327686

Sponsor: NRG Oncology

Enrollment: 240

Rationale: While the SWOG PROBE trial (S1931) is currently evaluating the role of cytoreductive nephrectomy in patients with metastatic renal cell carcinoma (mRCC) receiving immunotherapy, a significant number of patients presenting with mRCC are either not candidates for surgical intervention or refuse surgical resection. There are data suggesting that stereotactic ablative radiotherapy (SABR) to the primary tumor in RCC can be safe and highly effective. In addition, there are hypothesized to be immunomodulatory effects of SABR, but

these have not been studied prospectively in RCC. Thus, the SAMURAI study aims to test the ability of SABR to adequately treat the primary tumor with local cytoreduction and potentially modulate immunotherapy.

Study Design: This randomized Phase II multicenter study enrolls patients with a histologically or cytologically proven diagnosis of RCC with radiographically node-positive or metastatic disease, with IMDC intermediate or poor risk disease. Patients must be candidates to receive standard of care therapy with either nivolumab plus ipilimumab or an immune checkpoint inhibitor (CPI) and vascular endothelial growth factor tyrosine kinase inhibitor (VEGF TKI). The primary renal tumor must measure 8 cm or less, and cytoreductive nephrectomy should be deemed as not recommended by the investigator or should be declined by the patient. Patients are ineligible for enrollment if planned therapy would be definitive such that it would render the patient without extra-renal measurable disease. Patients must not have untreated or unstable brain metastases, and cannot have had prior systemic therapy for mRCC, though prior chemotherapy for a different cancer completed 3 years prior to registration is permitted.

Patients who are enrolled to the study will be randomized to Arm A, consisting of standard of care immunotherapy or CPI + VEGF TKI, or Arm B, in which patients receive standard of care of immunotherapy or CPI + VEGF TKI as well as SABR delivered in 3 fractions for a total of 42 Gy over 1-3 weeks.

Endpoints: The primary endpoint of this study is nephrectomy and radiographic progression-free survival (nrPFS). Key secondary endpoints include safety, objective response rate (ORR), overall survival, treatment-free survival, and second-line therapy-free survival. The rate of cytoreductive nephrectomy per arm will also be captured as a secondary endpoint.

Comments: For years, cytoreductive nephrectomy was a clinical standard for patients with mRCC, supported by randomized clinical trials in the cytokine era of mRCC treatment. Since then, as systemic therapy for mRCC evolves, the pendulum has swung away from cytoreductive nephrectomy based on trials in the VEGF TKI era of mRCC treatment. While the S1931 PROBE study will further evaluate the role of cytoreductive nephrectomy in the current era of mRCC treatment, the role of radiation therapy to the primary tumor is a more recent question. In recent years, the role of radiation therapy in mRCC has been better appreciated, but still requires rigorous study. The SAMURAI study serves as a complement to PROBE, in that this Phase II study enrolls patients who are not candidates for nephrectomy or have declined it. Both the PROBE and SAMURAI studies will provide important information on the interplay between immunotherapy, treatment modality, and the primary tumor. Both studies also face challenges in optimal accrual. For SAMURAI, patients must have primary tumors less than 8 cm in size and be considered non-candidates for surgical resection. At the same time, patients must have adequate end organ function to receive systemic therapy on the study. Thus, finding the patient who best meets enrollment criteria may be difficult. Nevertheless, this cooperative group trial is addressing an important question in a rigorous way, which must be commended.

CONFLICT OF INTEREST

Mamta Parikh

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