TPS4616 Poster Session

A randomized trial of radium-223 dichloride and cabozantinib in patients with advanced renal cell carcinoma (RCC) with osseous metastases (RADICAL/Alliance A031801).

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Background: Osseous metastases (OM) occur in approximately 30% patients with advanced RCC. Despite therapeutic advances, OM are associated with poor survival and risk of symptomatic skeletal events (SSEs). Cabozantinib targets multiple tyrosine kinases, including vascular endothelial growth factor (VEGF) receptors and MET (Mesenchymal-Epithelial Transition factor), which are overexpressed in OM, contributing to cabozantinib's enhanced bone activity. Radium-223, an alpha-emitting bone-seeking radioisotope, prolongs survival in men with metastatic castration-resistant prostate cancer to the bone. Building on this therapeutic approach targeting OM, our pilot study of radium-223 with VEGF inhibition in RCC with OM has also shown safety, improvement in circulating bone turnover markers, and early efficacy (McKay et al, CCR 2018). To address the unmet need to improve SSE rates and outcomes in RCC and OM, we designed a study investigating cabozantinib with or without radium-223 in patients with RCC with OM (NCT04071223). **Methods:** This is an open-label, multicenter randomized phase-2 study. Key inclusion criteria include metastatic RCC of any histology with $\geq$1 OM, at least 1 OM without prior radiation, any number of prior therapies, and Karnofsky performance status $\geq$ 60%. Use of a bone protecting agent is required unless contraindicated. Patients are randomized 1:1 to cabozantinib with (Arm A) or without (Arm B) radium-223. The starting dose of cabozantinib for Arm A is 40 mg by mouth daily to be escalated to 60 mg daily after cycle 1 (1 cycle = 28 days) if no persistent grade 2 or grade $\geq$3 toxicity. Radium-223 is administered at a fixed dose of 1.49 microcurie/kg IV every 28 days x 6 doses. The starting dose for cabozantinib in Arm B is 60 mg daily. The primary endpoint is SSE-free survival. Secondary endpoints include safety, progression-free survival, overall survival, time to first SSE, objective response rate, time to subsequent anti-cancer therapies, quality of life (QoL) measures, and correlative analyses including liquid biopsy and tumor tissue analysis. The study is designed to have 85% power to detect an improvement in 6-month SSE-free survival rate from 65% to 78% with one-sided α = 0.05 significance. To ensure 124 evaluable patients, target accrual is 134 (67 per arm). The group-sequential design includes a safety run-in and an interim analysis for futility when 50% of the expected number of events have been observed. The safety run-in, performed in the first 12 patients randomized to combination therapy, did not demonstrate dose limiting toxicities. Final data analysis will occur when 99 events have been observed. The study was activated in July 2020 and accrual is ongoing throughout the National Clinical Trials Network (NCTN). Continued site participation and enrollment are essential to evaluate this therapeutic strategy. Clinical trial information: NCT04071223. Research Sponsor: None.