A Randomized Trial of Radium-223 Dichloride and Cabozantinib in Patients with Advanced Renal Cell Carcinoma with Bone Metastases (RADICAL / Alliance A031801)

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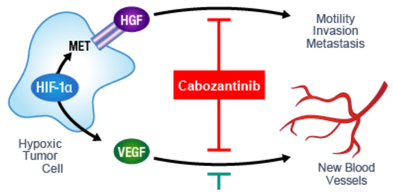
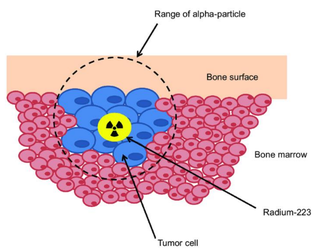
Background:

- Bone metastases are prevalent in 30% of patients with advanced RCC.
- Patients with bone metastases have worse prognosis and are at risk of SSEs which are associated with significant morbidity.
- Cabozantinib has improved survival in patients with metastatic RCC and has enhanced activity in bone.





- Radium-223, an alpha-emitting radioisotope with natural bone-seeking proclivity, has been shown to prolong survival in men with prostate cancer.
- We previously conducted a pilot study in patients with metastatic RCC treated with radium-223 and VEGF inhibitors showing safety and declines in markers of bone formation and resorption with the combination (Table 1) (McKay et al, CCR 2018).

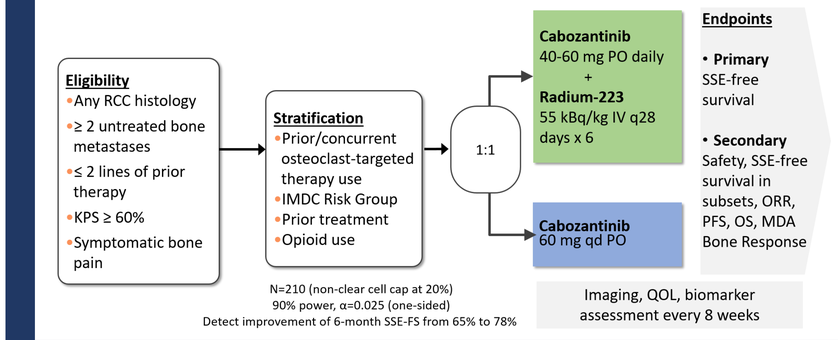
Table 1.

	Baseline levels (median, IQR)	Maximum decline (median, IQR)
CTX (ng/mL)	0.43 (0.21, 0.6)	−40.7 (−59.6, −32.4)
PINP (µg/mL)	45.5 (30.25, 65.75)	−59.3 (−66.7, −48.4)
BALP (µg/mL)	11 (9.1, 16)	−29.2 (−42.5, −11.7)
OC (ng/mL)	16 (12.25, 18.75)	−50 (−61.3, −40.6)
NTX (nmol/L BCE)	14.9 (11.3, 21.3)	−32.8 (−48, −12.3)

The RADICAL trial is currently OPEN for accrual.

Visit www.CTSU.org to start the activation process.

Study Schema



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RCC=Renal cell carcinoma, SSE=Symptomatic skeletal event, VEGF=Vascular endothelial growth factor, KPS=Karnofsky performance status, PO=By mouth, IV=Intravenous, PFS=Progression-free survival, OS=Overall survival, QOL=Quality of life.

Methods:

- **Design:** Open-label, randomized phase 2
- **Eligibility:**
  - Any RCC histology (non-clear cell 20%)
  - ≥ 2 untreated bone lesions
  - ≤ 2 lines of prior therapy
  - KPS ≥ 60%
  - Symptomatic bone pain (defined as a prior SSE or use of analgesics)
- **Treatment:** Cabozantinib with (Arm A) or without (Arm B) radium-223. Starting dose of cabozantinib for Arm A is 40 mg PO daily to increase to 60 mg after cycle 1 (1 cycle=28 days) if no persistent grade 2/grade ≥3 toxicity. Radium-223 dose is fixed at 55 kBq/kg IV every 28 days x 6.
- **Primary Endpoint:** SSE-free survival.
- **Secondary Endpoints:** Safety, PFS, OS, QOL, measures, and correlative analyses including liquid biopsy studies and tumor tissue analysis.
- **Statistical Plan:** 90% power to detect an improvement in 6-month SSE-free survival rate from 65% to 78% (one-sided α=0.025). To ensure 191 evaluable patients, target accrual is 210. This design includes a safety run-in and an interim analysis for futility.