TPS5094 General Poster Session (Board #42E), Mon, 8:00 AM-11:45 AM

A phase II trial of cabozantinib (Cabo) in patients (pts) with castrate-resistant prostate cancer (CRPC) metastatic to bone (NCT01428219).

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Background: MET overexpression predicts prostate cancer invasion and bone metastasis; inhibition of MET/VEGF pathways has synergistic activity in CRPC (Knudsen et al. Adv Cancer Res 2004; Aftab et al. Clin Transl Oncol 2011). Cabo is a small molecule that inhibits multiple receptor tyrosine kinases, including MET and VEGFR2. A phase II randomized discontinuation trial of Cabo showed clinical activity in CRPC, including reduction of soft tissue lesions, prolongation of progression-free survival (PFS), resolution of bone scans, and reductions in bone turnover markers, pain and narcotic use (Smith et al, JCO 2013). To further define the activity of Cabo in pts with CRPC and bone metastases, we launched a phase II trial to characterize the effects of Cabo on bone metabolism and tumor activity in prostate cancer bone lesions. We hypothesize that the clinical activity of Cabo correlates with measurable pharmacodynamic effects on bone micro-environment. **Methods:** After informed consent, chemotherapy-naive pts with progressive CRPC and bone metastases accessible to CT-guided biopsy, adequate performance status/organ function, are treated with Cabo 60 mg once daily. Primary endpoint: proportion of pts progression-free (PF) at 12 weeks. Secondary endpoints: safety, PFS, response proportion/duration, PSA response, PSA time-to-progression. A Simon's two-stage mini-max design permits early termination after the first 27 evaluable pts in case of unfavorable results. Alternatively, up to 46 evaluable pts will be accrued. Cabo would not be of interest if the 12-week PF proportion is <0.45; it would be of definite clinical interest if the 12-week PF proportion is >0.65 (5% type I error, 85% power). Perfusion/diffusion-weighted MRI (parametric response maps) and bone lesion biopsies are required at baseline and 6 weeks after starting Cabo. Doxycycline is administered prior to bone biopsy for bone labeling. Bone cores are sent for dynamic histomorphometry and immunohistochemistry (phospho-MET/MET, phospho-VEGFR2/VEGFR2, phospho-Akt/Akt). Serum is collected at several time-points to measure markers of bone metabolism. 13 of 27 first-stage pts have been enrolled and started Cabo. Clinical trial information: NCT01428219.