

Assessing XL184 treatment in metastatic prostate cancer to the bone by diffusion mri

Jean-Christophe Brisset¹, Benjamin A Hoff¹, Stefanie Galbán², Benjamin Lemasson¹, Alnawaz Rehemtulla², Craig J Galbán¹, and Brian D Ross¹

¹Department of Radiology, University of Michigan, Ann Arbor, Michigan, United States, ²Department of Oncology, University of Michigan, Ann Arbor, Michigan, United States

Purpose: Bone metastases occurs in more than 90% of patients with advanced prostate cancer¹. This study aims to follow the effectiveness of an oral pan-tyrosine kinase inhibitor, the Cabozantinib (XL184) after one week of treatment in a prostate bone metastasis model. Cabozantinib strongly binds to and inhibits several tyrosine receptor kinases. Specifically, Cabozantinib appears to have a strong affinity for the hepatocyte growth factor receptor (Met) and vascular endothelial growth factor receptor 2 (VEGFR2), which may result in inhibition of tumor growth and angiogenesis and tumor regression. Cabozantinib is not currently approved by the US Food and Drug Administration (FDA) to treat patients but is advancing in Phase 2 trials to evaluate the therapeutic benefit on castrate-resistant prostate cancer metastatic to the bone. Traditional volumetric based approaches for response assessment are inadequate for skeletal involved tumors. Diffusion-weighted MRI (DW-MRI) has been demonstrated as a biomarker of tumor response to chemotherapy. The ability of DW- MRI to serve as a biomarker of response resides in its ability to detect alterations in the thermal motion of water molecules at the cellular level. These changes occur as a result of a decrease in tumor cellular density consequent to cell death following an effective therapy. Our goal was to evaluate DW-MRI for detection and quantification of changes in tumor tissue during therapy.

Materials et methods: Human prostate cancer (PC3) cells were implanted by direct intra-tibial injection into male SCID mice, which serves as a model for prostate bone metastases². MR experiments were performed on a 9.4T horizontal bore magnet using a quadrature 20 mm volume coil with the leg securely fastened within the coil to reduce motion. Upon detection of a tumor volume of $\sim 10\text{mm}^3$, animals were randomly distributed into 2 treatment groups: XL184, 30 mg/kg oral gavage once a day for 7 days (qdx7; N=7) and control (N=5). Animals were imaged by DW-MRI using the following sequence: spin-echo, TR/TE 4000/37, FOV 20x20mm², b-values 120-1200 s/mm², slices thickness 0.5 mm and 40 slices. Tumor volume and cellularity were monitored using the low-b T2-weighted image and the apparent diffusion coefficient (ADC), respectively. ADC values for each voxel were calculated analytically using the two diffusion-weighted images. Tumor volume and ADC measurements were obtained pre-treatment and on days 1, 4, 7, 11, 14 post-treatment initiation and then twice weekly. Percent change in tumor volume and ADC were plotted as a function of time. Animals were removed from the study when the tumor reached a percent increase of 400% (5x the initial tumor volume). Group comparisons in MRI metrics were determined using a unpaired *Student t*-test.

Results: In Fig 1, mice treated by XL184 had significantly reduced tumor growth rate compared to control mice and resulting in smaller tumor volumes 1 week post treatment completion ($p=0.05$). As shown in Fig 2, the treated group was found to have an increase in ADC immediately following the completion of therapy. ADC values in the control group were stable in the $\pm 5\%$ range. In Fig. 2, representative color overlay of ADC maps on low b-value DW images at day 7 reveals elevated ADC values in the treated mouse (upper image) as compared to the control mouse (lower image).

Conclusion: XL184 treatment was effective as assessed by anatomical and DW-MRI. Results presented herein demonstrated the potential of using quantitative ADC maps to rapidly assess tumor response. DW-MRI is useful as an imaging biomarker of skeletal prostate metastasis treatment response.

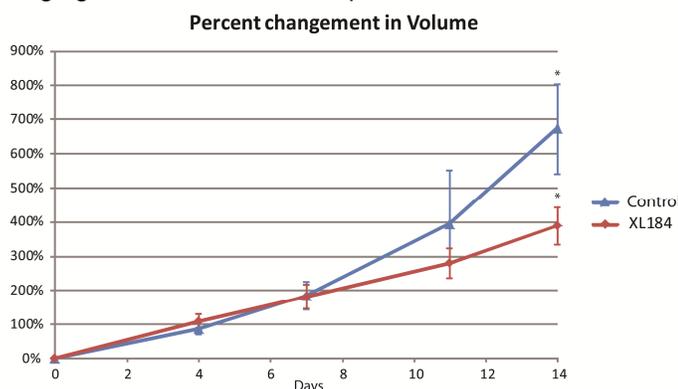


Fig 1: Evolution of the percentage change evolution in tumor volume. Mean +SE.

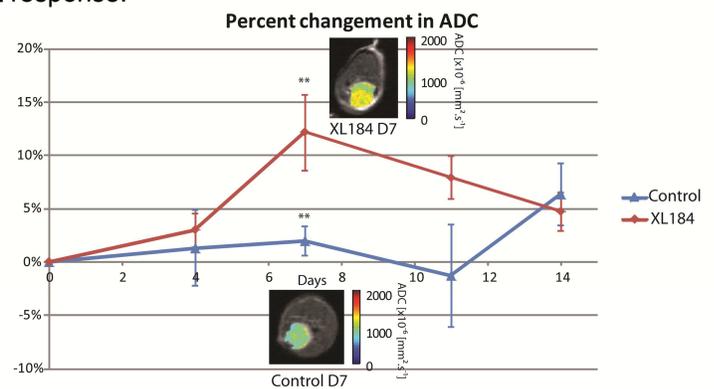


Fig 2: Evolution of the percentage change evolution in ADC. Mean +SE $p<0.05$ reached after D7 only for XL184 compared to control.

References: 1.Carlin BI, *Cancer*. 2000;88:2989-2994.2.Lee KC, *Cancer Res*. 2007;67(8):3524-3528