Non-Invasive Imaging Biomarkers of Tumor Response to XL184 Therapy

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Target Audience: Researchers interested in imaging biomarkers and targeted therapies

Purpose: Clinical response criteria (RECIST 1.1) considers boney metastases measuring >10mm without soft tissue involvement as unmeasurable. The clinical need for accurate therapeutic response measures is more pressing with the introduction of targeted therapies into standard of treatment. XL184 is a novel tyrosine kinase inhibitor that exhibits activity against mainly MET and VEGFR-2.[1] We evaluated DW-MRI and CT pre- and post-therapy on a mouse model of bone-metastatic prostate cancer to assess early treatment response to this therapy. The therapeutic effect of XL184 was observed via several readouts, with mean tumor ADC increasing significantly over controls by day 3 post-therapy.

Materials and Methods:

Animal Model: Half a million human prostate cancer cells (PC3) were implanted via direct intra-tibial injection in male SCID mice. Once tumor volumes reached approximately $10mm^3$, animals were administered either 30mg/kg XL184 or vehicle (Control; 150ul 10% DMSO) daily via oral gavage for 21 days.

Imaging: Acquisition of diffusion MRI was performed pre-treatment and twice weekly thereafter using a horizontal-bore 9.4T *DirectDrive* system and quadrature mouse head RF coil. DW images were obtained using a multi-slice spin-echo sequence with navigator echo and the following parameters: isotropic diffusion weighting of 120 and 1200 s/mm^2, TR/TE = 4000/37, slice thickness = 0.5mm, matrix size = 128x64, and 1 average. Dynamic contrast-enhanced (DCE-) MRI was performed pre- and one week post-treatment with the following parameters: TR/TE = 25/5ms, slice thickness = 0.5mm, matrix size = x128, 1 average and temporal resolution of 10 s for 15 min. X-ray CT imaging was also performed pre-treatment and then weekly until the end of the study with the following parameters: 80kVp, 0.5mA, isotropic voxel size = 56um.

Statistics: All data, except for K^{trans}, was presented as the percent change of the tumor mean from pre-treatment values. Significant difference between groups was assessed using an un-paired two-tailed Student's t-test.
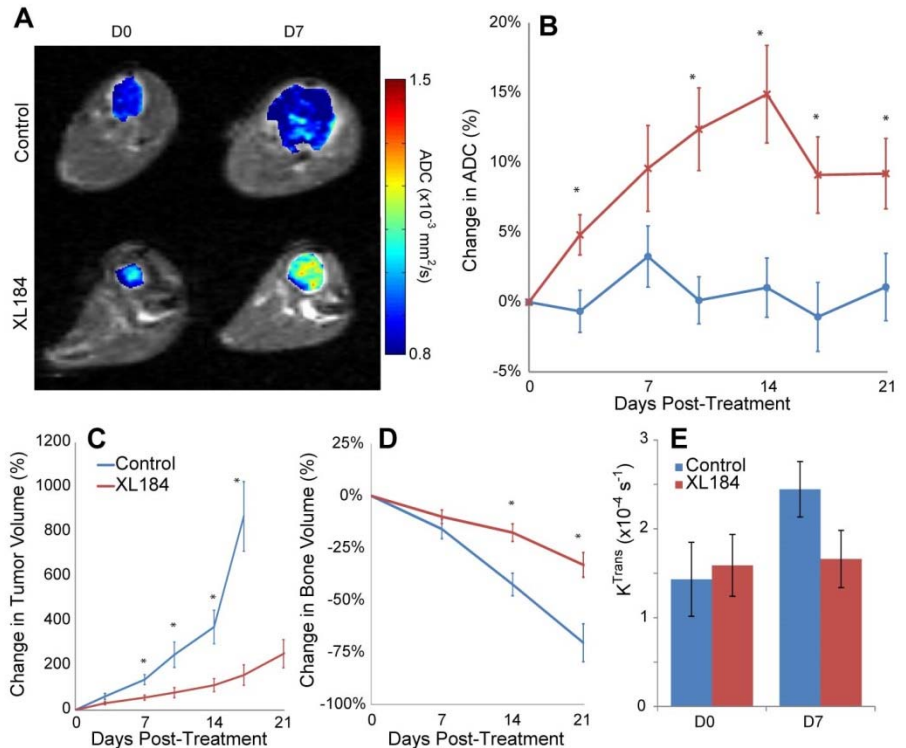

Figure 1: ADC increased in the XL184 group, seen in the overlays (A) and time plot (B), with significance starting at day 3 post-Tx (p=0.015). Mean group percent change (C) tumor volume and (D) bone volume show therapeutic inhibition of both tumor growth and bone erosion. Mean tumor K^{Trans} (E) shows maintenance of low vascular leakiness below controls. * indicates significant difference between groups and error bars represent the SEM.

Results: As shown in Figure 1, mean tumor ADC increased significantly by day 3 post-treatment initiation in the XL184 group above controls (p<0.02) with significant differences in tumor volume observed on day 7 (p<0.01). As determined by CT, tumor bone resorption was diminished in the treated group with significant differences from controls observed on day 14. XL184 therapy maintained pre-treatment K^{Trans} values by day 7 post-treatment initiation, which was significantly lower than controls (p<0.05).

Discussion: PC3 cancer cells are well-known to exhibit high tumorigenicity and osteolytic potential as evidenced by the fast tumor growth and bone erosion in the control group. XL184 treatment targets both MET and VEGFR-2, which are vital to the tumor's proliferation and invasion, resulting in the growth inhibition seen in the volume plot. Both c-Met and VEGF signaling stimulate angiogenesis, and the observed low values of K^{Trans} from DCE-MRI indicate that XL184 successfully inhibited neovascular growth. ADC was also observed to increase post-treatment, indicating a decrease in tumor cellularity via tumor cell death.[2] Overall, XL184 treatment response was observed as early as 3 days post-therapy (ADC), and ultimately resulted in tumor growth inhibition. MRI provided imaging biomarkers relevant for the early detection of metastatic bone cancer response.

References:

1. Smith, D.C., et al., *Cabozantinib in patients with advanced prostate cancer: results of a phase II randomized discontinuation trial.* J Clin Oncol, 2013. **31**(4): p. 412-9.
2. Ross, B.D., et al., *Evaluation of cancer therapy using diffusion magnetic resonance imaging.* Mol Cancer Ther, 2003. **2**(6): p. 581-7.