Hyperpolarizied 13C MRSI is a better predictor of survival than tumor size in treated glioblastoma

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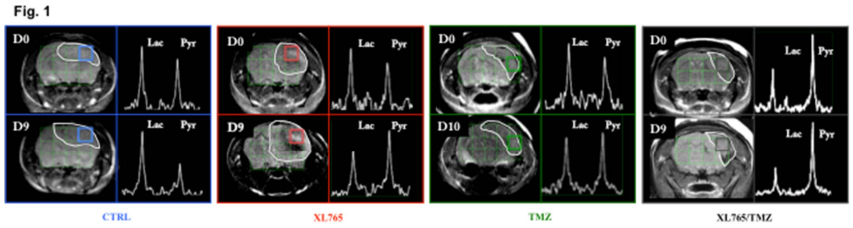
Introduction Current standard of care for glioblastoma (GBM) is surgical resection, radiation and treatment with Temozolomide (TMZ). However, resistance to current therapy and recurrence is common and expected. Because PI3K/Akt/mTOR signaling pathway is activated in ~88% of GBM [1], it represents an important alternative therapeutic target. Previous *in vivo* studies in orthotopic rat models have revealed that response to the treatment with an mTOR inhibitor or with TMZ can be monitored by the decreased production of hyperpolarized lactate [2-4]. In order to prepare for an upcoming clinical trial, the goal of this study was to expand upon previous work and to confirm that previous findings are reproduced in different model systems, different genetic background and with a novel PI3K/Akt/mTOR inhibitor. We used hyperpolarized *in vivo* ^{13}C MRSI and ^{1}H MRS, and *ex vivo* ^{1}H HR-MAS to monitor the effect of the dual PI3K and mTOR inhibitor XL765 (SAR245409) and TMZ alone or in combination in GS-2 tumors in mice.

Materials and Methods Athymic nu/nu mice (6 weeks old) were injected intracranially with 3x10^5 GS-2 cells [4]. Once tumors reached a diameter of ~3mm, animals were treated p.o. with either XL765 [5], or TMZ, or TMZ plus XL765 or 10mM HCl as a control vehicle. MRI studies were performed using a vertical wide bore Varian (Agilent) 600MHz scanner. [1-^{13}C]-pyruvic acid containing 15mM trityl radical OX063 was hyperpolarized using a HyperSense DNP polarizer, followed by dissolution and injection through an i.v. tail-vein catheter over 12s. ^{13}C MRSI spectra were recorded 17s after injection using 2D-CSI (TE/TR=0.58/66ms, frequency dimension=256, phase dimension=16x16) and processed using Sivic [5]. Peak integrals were normalized to normal brain and pre-treatment values. ^{1}H MRS spectra were recorded using PRESS sequence (TE/TR=20/4000ms, voxel=2x2x4mm, 256-512) and analyzed using jMRUI. In addition biopsy samples from excised tumors at the end of the study were investigated using ^{1}H HR-MAS. HR-MAS spectra were recorded on Varian (Agilent) 500MHz using the CPMG sequence.



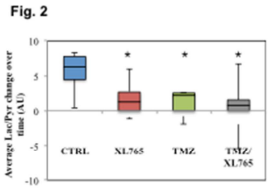
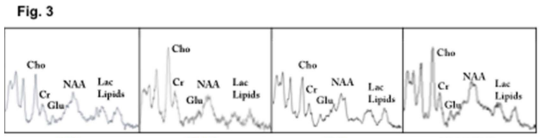
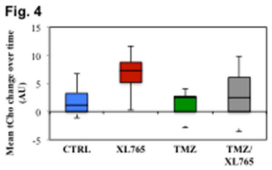


Fig. 1: shows axial anatomic images at day 0 (upper panel) and last day of treatment (lower panel). Each panel (left to right) shows the chemical shift voxels overlaid on the anatomic image and the corresponding ^{13}C MRSI spectrum of the tumor voxel. *Fig. 2*: Average Lac/Pyr change during treatment.





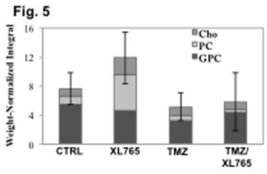


Fig. 3: ^{1}H MRS spectra of the tumor voxels at the last day of treatment. *Fig. 4*: In-vivo ^{1}H MRS average total choline change during treatment. *Fig. 5*: *ex-vivo* ^{1}H HR-MAS average of the choline metabolites.

Results and discussion *In vivo* ^{13}C MRSI (*Fig. 1, 2*) exhibits a significant drop in average ^{13}C hyperpolarized Lac/Pyr ratio as a result of treatment with XL765 and TMZ alone or in combination compared to control group. The findings with regard to TMZ confirm previous observations and show that our findings are independent of model. ^{1}H MRS spectra (*Fig. 4, 5*) indicate a trend to increase in total choline level as a result of treatment with XL765 but demonstrate that choline does not provide a reliable biomarker of response to therapy.

Fig. 6 shows the evolution of tumor size during treatment. *Fig. 7* illustrates significantly longer survival in the case of treatments with XL765, TMZ and their combination. Importantly our data show that the temporal evolution of the Lac/Pyr ratio differs significantly between control and treated mice, and therefore predicts the survival prior to a detectable change in tumor size. Upon clinical transition, this approach could assist the treatment decision-making process based on individual response to drug at early time points when tumor size is still unchanged.

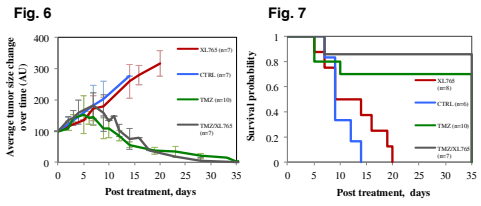


Fig. 6: Tumor size change during treatment (% D0).
Fig. 7: Kaplan-Meier survival plot.

References 1. CGARN, *Nature*, **2008**, 455(7216). 2. Park I., *JMRI*, **2011**. 3. Park I., *Cancer Res.*, **2014**. 4. Chaumeil M.M., *Neuroimage*, **2012**. 5. Prasad G., *Neuro-Oncology*, **2011**. 6. Crane J.C., *Inter. J. Biomed. Imag.* **2013**.

Acknowledgments The study was supported by NIH R01CA154915.