



# Dynamic contrast-enhanced magnetic resonance perfusion weighted imaging (DCE-MRI) and diffusion weighted imaging (DWI) for pharmacodynamic evaluation of carboxyamidotriazole orotate (CTO) and temozolomide in malignant glioma

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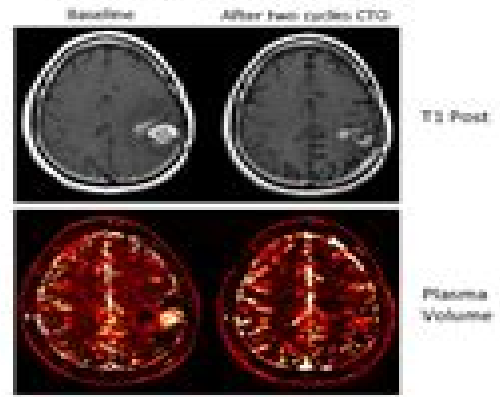
## Background

- CTO is an oral inhibitor of non-voltage-dependent calcium signaling
- Modulates several pathways including EGFR, MEK, RAS, HDAC, HSP90, WNT/ $\beta$ -catenin, Akt, ERK, VEGF, Bcr-Abl
- To determine in human pharmacodynamic effects of this drug, we evaluated advanced MRI parameters in an ongoing phase I trial of combined CTO and adjuvant temozolomide for recurrent malignant glioma

## Methods

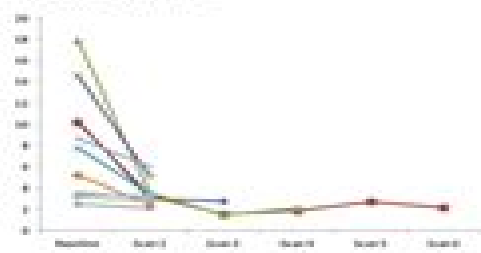
- Patients underwent DCE-MRI and DWI at baseline and after every two 28-day cycles
- Changes in imaging parameters were evaluated with volumetric histogram analysis of the tumor (NordICE v2.3, Bergen, Norway)
- Assessed plasma volume (Vp), vascular permeability (Ktrans), and diffusion (ADC)
- Analyzed normalized results (tumor compared to normal brain tissue in each patient) with Mann-Whitney u tests

## Example of Tumor Response with Decreased Perfusion in GBM

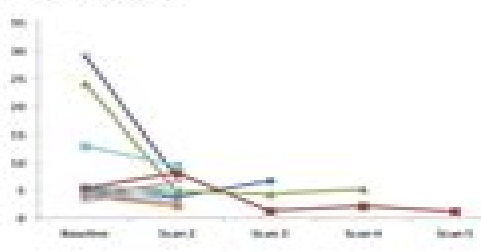


## Change in parameters in all patients:

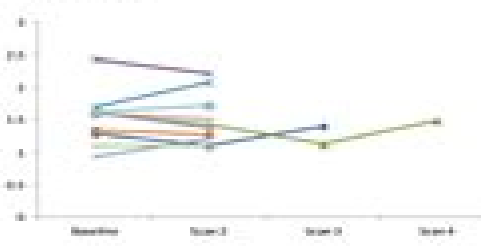
### Plasma Volume



### Permeability



### Diffusion



## Results- Patient Characteristics

- N=11 to date (9 Men, 2 Women)
- Histology: 9 GBM; 2 Grade III
- MGMT status:
  - 4 methylated
  - 4 unmethylated
  - 3 unknown
- Prior treatment:
  - All patients had prior surgery, RT, and TMZ
  - 3 Bevacizumab failures
- CTO dose range 219-812.5 mg/m<sup>2</sup>/day
- Includes 2 pts with radiographic response on standard MRI.

## Results- Imaging Parameters

Baseline vs Initial Follow-up (after two cycles of CTO)

	Baseline	Follow-up	p-value
Plasma Volume	1.00	0.60	0.00
Permeability	1.22	0.69	0.05
Diffusion	1.00	0.50	0.00



\* All values are normalized and represent ratios of tumor to normal tissue

## Conclusions

- Early Vp changes seen in all pts, providing proof-of-concept that non-voltage-calcium channel blockade results in decreased blood perfusion in TMZ-refractory gliomas.
- Decreases in Vp were more apparent than in Ktrans, suggesting effects that are distinct from bevacizumab-induced VEGF blockade.
- Responders seemed to have higher baseline perfusion and permeability, requiring further investigation as potential biomarkers.
- Limitations: small number of pts, lack of perfusion in some scans.
- DCE-MRI is a useful tool to determine pharmacodynamic effects in early drug development.

# Dynamic Contrastenhanced Magnetic Resonance Imaging In Oncology

**Jin-Ying Zhang**



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