Phase IB trial of carboxyamidotriazole orotate (CTO) and radiotherapy with concurrent and adjuvant temozolomide in newly diagnosed glioblastoma

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Background

- CTO is an oral inhibitor of non-voltage-dependent calcium signaling that simultaneously modulates several receptor-mediated calcium-dependent signaling pathways, including EGFR, MEK, RAS, HDAC, HSP90, WNT/B-catenin, Akt, ERK, VEGF and Bcr-Abl. (Kohn, 1997; Berlin, 1997; Corrado 2012; Karmali, 2013).
- A single-agent phase I trial determined the maximum tolerated dose (MTD) at 427 mg/m2, with a safe toxicity profile (ASCO 2013; Taylor, 2015).
- A phase IB dose escalation of CTO with temozolomide (TMZ) for recurrent malignant glioma (MG) found therapeutic brain tissue concentrations and early evidence of activity, with radiographic responses and median survival of 15 months (ASCO 2014), prompting this newly diagnosed disease study. The recommended Phase II dose of CTO is 370 mg/m^2/day.

Methods

Primary Objective:

- Determine safety and tolerability of CTO in combination with standard radiation (RT) and concomitant TMZ followed by CTO combined with adjuvant TMZ in newly diagnosed GBM and other MG

Secondary/Exploratory Objectives:

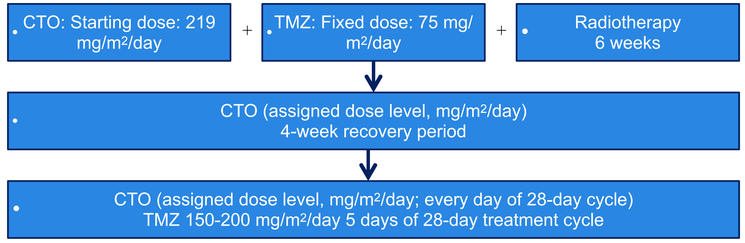
- Tumor response according to Macdonald criteria
- Determine PKs of CTO and TMZ
- Investigate effect of CTO on tumor growth based on tumor genotype

Key Inclusion Criteria

- GBM or MG
- ECOG 0-2
- Age ≥ 18
- Life expectancy ≥ 8 weeks
- Baseline MRI within 14 days
- Stable dose steroids; no CYP3A4 inhibitors or inducers

Table 1: Summary of Cohorts	
Cohort 1 (219mg/m^2/day), n=	3
Cohort 2 (285mg/m^2/day), n=	3
Cohort 3 (370mg/m^2/day), n=	6
Cohort 4 (481mg/m^2/day), n=	3
Total Enrollment: 15 Patients	

Study Design: Following a 3+3 design, pts were enrolled to receive escalating doses of daily CTO (219-481mg/m2) added to standard GBM RT regimen (60 Gy concurrent with TMZ 75 mg/m^2 daily), followed by adjuvant TMZ (150-200 mg/m^2 x 5/28 days).



References:

- Berlin, J., et al, *J. Clin Oncol* 1997, 15: 781-789
- Corrado, C., et al, *PLos ONE* 2012, 7: 1-13
- Karmali, RA, et al, Mol Cancer Ther 12:11s,2013, Abs A233
- Kohn E.C., et al, *J. Clin Oncol* 1997, 15: 1985-1993.
- Taylor M.H. et al, J. Cancer Ther 2015, 6: 322-333

Results

- ChemoRT well tolerated at CTO doses of 219-481 mg/m^2, with no dose-limiting toxicities (DLT) observed during the DLT period
- Late toxicities developed beyond the DLT observation period (final weeks of RT or 4-week recovery period: Gr 3 febrile neutropenia (N=2), gr 4 neutropenia (N=1), gr 4 platelets (N=1) and gr 3 ALT/AST (N=1).
- Halt in dose escalation at 481 mg/m^2 (declared the maximum administered dose, MAD) and expansion of a lower dose level (370 mg/m^2).
- PK data confirmed therapeutic levels starting at 219 mg/m^2 (Figure 1)
- Efficacy evaluation is ongoing, with one confirmed partial response and stable disease for 9+ cycles. (Figure 2)
- 10 of 15 patients had molecular profiling with next generation exon sequencing (Table 2)

Table 2: Patient characteristics	N(%)
Median Age (range)	58 (24-78)
Sex	
Male	7 (47%)
Female	8 (53%)
Histology (WHO Grade)	
GBM (IV)	14 (93%)
High Grade Astrocytoma (III/IV)	1 (7%)
MGMT Status	
Methylated	3 (33%)
Unmethylated	6 (67%)
IDH1 mutant (R132H, R132C)	2 (20%)
TERT promoter variant (n=5 1295228C>T; n=1 1295250C>T)	6 (60%)
EGFR amplification (22-36 fold)	4 (40%)
TP53 mutation (M237I/M246T, R175H/R342X, S127P)	3 (30%)
PTEN mutation (D326Y, Q261X, E43fs)	3 (30%)
ATRX mutation (R2407*, F888fx, R840fs, duplication)	4 (40%)

Figure 1: CTO pharmacokinetic profile. Dose Proportionality of AUC_{0-8} (1A), AUC-24 and Cmax following multiple-dose administration of CTO with quadratic nonlinear regression line

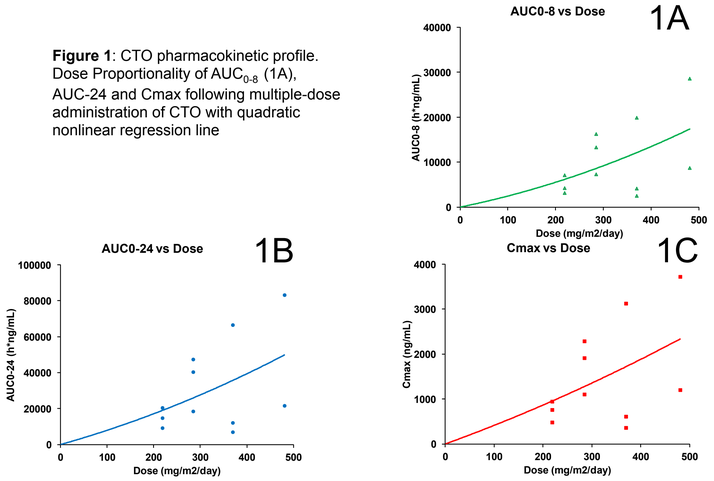


Figure 2: Radiographic partial response to CTO: Axial T1 post-contrast sequences at baseline and pre-cycle 7. Patient remains progression-free on stable dose of CTO 370 mg/m^2/day for 9+ cycles.

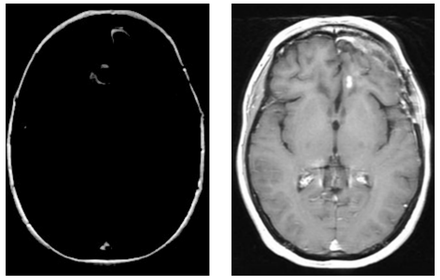


Table 3: All Toxicities, Regardless of Attribution (patients who completed RT as of 1/15/2015, N=12).

Table 3: Toxicity by Organ Class	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade ≥3	Overall
Fatigue	5 (41.7%)	3 (25.0%)	0	0	0	0	8 (66.7%)
Mucositis	1 (8.3%)	0	0	0	0	0	1 (8.3%)
Pyrexia	1 (8.3%)	0	0	0	0	0	1 (8.3%)
Gastrointestinal disorders	3 (25.0%)	1 (8.3%)	1 (8.3%)	0	0	1 (8.3%)	5 (41.7%)
Nausea	2 (16.7%)	0	1 (8.3%)	0	0	1 (8.3%)	3 (25.0%)
Constipation	1 (8.3%)	1 (8.3%)	0	0	0	0	2 (16.7%)
Abdominal distension	1 (8.3%)	0	0	0	0	0	1 (8.3%)
Vomiting	1 (8.3%)	0	0	0	0	0	1 (8.3%)
Investigations	0	2 (16.7%)	1 (8.3%)	2 (16.7%)	0	3 (25.0%)	5 (41.7%)
ALT	0	2 (16.7%)	0	0	0	0	2 (16.7%)
Platelet decreased	0	1 (8.3%)	0	1 (8.3%)	0	1 (8.3%)	2 (16.7%)
AST	0	1 (8.3%)	0	0	0	0	1 (8.3%)
Alkaline phosphatase	1 (8.3%)	0	0	0	0	0	1 (8.3%)
Bilirubin	0	1 (8.3%)	0	0	0	0	1 (8.3%)
Liver function tests, NOS	0	0	1 (8.3%)	0	0	1 (8.3%)	1 (8.3%)
Neutrophil decreased	0	0	0	1 (8.3%)	0	1 (8.3%)	1 (8.3%)
Nervous system disorders	5 (41.7%)	0	0	0	0	0	5 (41.7%)
Headache	2 (16.7%)	0	0	0	0	0	2 (16.7%)
Dysgeusia	1 (8.3%)	0	0	0	0	0	1 (8.3%)
Peripheral sensory neuropathy	1 (8.3%)	0	0	0	0	0	1 (8.3%)
Tremor	1 (8.3%)	0	0	0	0	0	1 (8.3%)
Skin and subcutaneous tissue	1 (8.3%)	2 (16.7%)	1 (8.3%)	0	0	1 (8.3%)	4 (33.3%)
Rash NOS	1 (8.3%)	1 (8.3%)	1 (8.3%)	0	0	1 (8.3%)	3 (25.0%)
Rash maculo-papular	0	1 (8.3%)	0	0	0	0	1 (8.3%)
Blood and lymphatic system	0	0	2 (16.7%)	0	0	2 (16.7%)	2 (16.7%)
Febrile neutropenia	0	0	2 (16.7%)	0	0	2 (16.7%)	2 (16.7%)
Anemia NOS	0	0	1 (8.3%)	0	0	1 (8.3%)	1 (8.3%)
Eye disorders	1 (8.3%)	0	0	0	0	0	1 (8.3%)
Vision blurred	1 (8.3%)	0	0	0	0	0	1 (8.3%)
Infections and infestations	1 (8.3%)	0	0	0	0	0	1 (8.3%)
Urinary tract infection	1 (8.3%)	0	0	0	0	0	1 (8.3%)
Injury, poisoning and procedural	0	1 (8.3%)	0	0	0	0	1 (8.3%)
Dermatitis radiation	0	1 (8.3%)	0	0	0	0	1 (8.3%)
Metabolism and nutrition disorders	1 (8.3%)	0	0	0	0	0	1 (8.3%)
Anorexia	1 (8.3%)	0	0	0	0	0	1 (8.3%)
Musculoskeletal and connective tissue	1 (8.3%)	0	0	0	0	0	1 (8.3%)
Peripheral swelling	1 (8.3%)	0	0	0	0	0	1 (8.3%)
Respiratory, thoracic and mediastinal	1 (8.3%)	0	0	0	0	0	1 (8.3%)
Pharyngitis	1 (8.3%)	0	0	0	0	0	1 (8.3%)

➢There were no DLTs or SAEs reported for the period of 1/15/15-5/15/15. There have been no toxic deaths; at the time of this analysis, all patients remain alive.

Conclusions

- CTO in combination with RT and TMZ is safe and well tolerated.
- The MAD dose was 481 mg/m^2/day and recommended phase II dose is 370 mg/m^2/day, although further evaluation of this dose level and longer follow up may be warranted.
- Efficacy evaluation is ongoing, with one confirmed partial response and stable disease for 9+ cycles. Given encouraging signals of activity, a randomized study is warranted.

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