Phase IB Trial of Carboxyamidotriazole orotate (CTO) and Radiotherapy with Concurrent and Adjuvant Temozolomide in Newly Diagnosed Glioblastoma

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Background

- Glioblastomas are associated with a dismal prognosis (Newly-diagnosed: PFS: 6-7m; OS: 14-19m)
- 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 (ASCO 2014), prompting this newly diagnosed disease study.

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 (Macdonald criteria)
- Determine PKs of CTO and TMZ
- Investigate effect of CTO on tumor growth based on tumor genotype

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).

Key Inclusion Criteria

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

Table 1: Cohorts/ dose levels
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

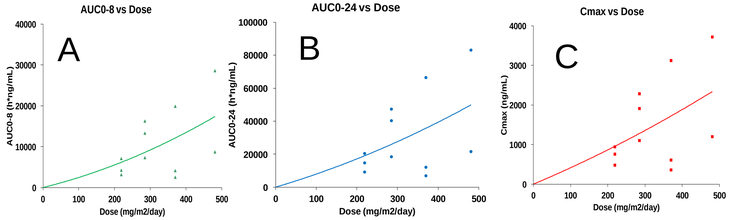
Results

Table 2: Patient characteristics (N=15)	N(%)
Median Age (range)	58 (24-78)
Sex Male Female	7 (47%) 8 (53%)
Histology (WHO Grade) GBM (IV) High Grade Astrocytoma (III/IV)	 14 (93%) 1 (7%)
MGMT Status Methylated Unmethylated	3 (33%) 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%)

Treatment

- A total of 15 pts were enrolled across multiple GBM molecular profiles (next generation sequencing done in 10 of 15 patients- Table 2)
- ChemoRT was well tolerated at CTO doses of 219-481 mg/m^2, with no dose-limiting toxicities (DLT) observed during the DLT period. Toxicities details are shown in Table 5
- 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). No toxic deaths observed
- 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). This dose was the recommended phase 2 dose (RP2D)

Fig.1: Pharmacokinetics data confirmed therapeutic levels starting at 219 mg/m^2 . Shown below: Dose Proportionality of AUC_{0-8} (A), AUC-24 (B) and Cmax (C) following multiple-dose administration of CTO with quadratic nonlinear regression line



Brain tumor penetration: Analysis of tumor tissue obtained in two patients undergoing surgical resection while on CTO demonstrated therapeutic concentrations

Table 3 Pt ID	Dose CTO mg/m^2/day	Plasma level (ng/ml)	Tissue level in enhancing tumor (ng/g)	Tissue level in non-enhancing tumor (ng/g)
004-68	285	213		1065
004-79	481	3460	5900	5500

Exploratory analysis of PFS and OS: Efficacy analysis is ongoing, with one confirmed partial response and stable disease for 21+ months. Four patients remain on single-agent CTO after completing 12 Cycles.

Table 4: Kaplan-Meier estimates		95% CI
Med PFS	15m	5.2- inf
1y-PFS	53%	23-75
Med OS	24m	15- inf
1y-OS	93%	61-99
Med Follow up of survivors	19m	

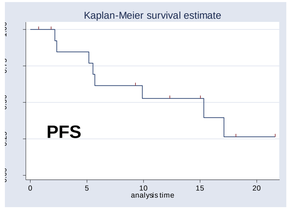


Fig. 2: Durable Radiographic Response. Axial T1 post-contrast MRI at baseline and after 21 months on treatment , showing near complete resolution of enhancing mass crossing the corpus callosum. This patient received chemo-RT with temozolomide and CTO 370 mg/m^2/day for 12 adjuvant cycles and then switched to single-agent CTO, remaining progression-free with a KPS of 90.

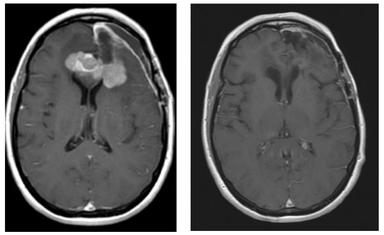


Table 3: All Gr 3-5 toxicities and Gr 1-2 toxicities developing in >1 pt, regardless of attribution

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade ≥3	Overall
Gastrointestinal disorders							
Nausea	5 (33.3%)	1 (6.7%)	1 (6.7%)	0	0	1 (6.7%)	7 (46.7%)
Constipation	3 (20%)	2 (13.3%)	0	0	0	0	5 (33.3%)
Diarrhoea	2 (13.3%)	0	0	0	0	0	2 (13.3%)
Vomiting	2 (13.3%)	0	0	0	0	0	2 (13.3%)
General disorders and administrative site conditions							
Fatigue	2(13.3%)	4(26.7%)	0	0	0	0	6 (40%)
Injury, poisoning and procedural							
Dermatitis radiation	4 (26.7%)	1 (6.7%)	0	0	0	0	5 (33.3%)
Investigations							
Platelet decreased	1 (6.7%)	3 (20%)	0	0	0	0	4 (26.7%)
ALT	0	2 (13.3%)	1 (6.7%)	0	0	1 (6.7%)	3 (20%)
White blood cell count decreased	1 (6.7%)	0	1 (6.7%)	0	0	1 (6.7%)	2 (13.3%)
Neutrophil count decreased	0	1 (6.7%)	0	1 (6.7%)	0	1 (6.7%)	2 (13.3%)
Nervous system disorders							
Headache	4 (26.7%)	0	0	0	0	0	4 (26.7%)
Convulsion	1 (6.7%)	1 (6.7%)	0	0	0	0	2 (13.3%)
Dysgeusia	2 (13.3%)	0	0	0	0	0	2 (13.3%)
Skin and subcutaneous tissue							
Rash NOS	2 (13.3%)	0	1 (6.7%)	0	0	1 (6.7%)	3 (20%)
Pruritus	1 (6.7%)	1 (6.7%)	0	0	0	0	2 (13.3%)
Eye disorders							
Vision blurred	2 (13.3%)	0	0	0	0	0	2 (13.3%)
Optic neuritis	0	0	1 (6.7%)	0	0	1 (6.7%)	1 (6.7%)
Infections and infestations							
Upper respiratory tract infection	2 (13.3%)	0	0	0	0	0	2 (13.3%)
Urinary tract infection	2 (13.3%)	0	0	0	0	0	2 (13.3%)
Metabolism and nutrition disorders							
Hypokalaemia	2 (13.3%)	0	0	0	0	0	2 (13.3%)
Musculoskeletal and connective tissue							
Back pain	2 (13.3%)	0	0	0	0	0	2 (13.3%)
Blood and lymphatic system disorders							
Febrile neutropenia	0	0	1 (6.7%)	0	0	1 (6.7%)	1 (6.7%)

Conclusions

- CTO in combination with RT and TMZ is safe and well tolerated.
- CTO crosses the blood-brain barrier, with therapeutic levels observed in brain tumor tissue.
- The MAD dose was 481 mg/m^2/day and RP2D is 370 mg/m^2/day.
- Exploratory efficacy evaluation suggests highly promising PFS and OS across multiple phenotypes; a randomized phase II study is planned.

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