Phase 1B Trial of Carboxyamidotriazole Orotate (CTO) Combined with Temozolomide for Recurrent Glioblastoma and Other Malignant Gliomas

Xuling Lin[1], Thomas J. Kaley[1], Elena Pentsova[1], Lisa M. DeAngelis[1], Mariza Daras[1], Igor Gavrilovic[1], Ingo Mellinghoff[1], Andrew McKeown[1], Malbora Manne[1], Jessica Hansen[1], Linda Bavisotto[2], Greg Gorman[3], Michael Lamson[4], Rashida A. Karmali[5], Antonio M. P. Omuro[1]

[1]Memorial Sloan Kettering Cancer Center; [2]Porta Clinica PLLC, [3]Samford University; [4]Nuventra Pharma Sciences; [5]Tactical Therapeutics

Background

- Glioblastoma (GBM) and other malignant gliomas (MG) exhibit aggressive spatial and molecular heterogeneity with multiple activated signaling pathways.
- Developing meaningful treatments is challenging due to blood-brain barrier/ drug delivery, chemoresistance, and tumor-induced immunosuppression.
- CTO is an oral inhibitor of non-voltage dependent calcium signaling that 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, Corrado 2012, Karmali 2013).
- CTO crosses the blood brain barrier, as demonstrated by higher drug concentrations in surgically resected tumor tissues compared to plasma.
- In preclinical studies, CTO has shown synergism with temozolomide (TMZ) and induced sensitivity to TMZ in unmethylated MGMT tumors (Karmali 2011, 2014).
- In a Phase I safety study (NCT01107522) in advanced solid tumors testing doses of 50-427mg/m2/day, CTO showed a safe toxicity profile, predictable pharmacokinetics and responses in various refractory tumors with different mutations (Taylor 2015).

Study Design

- **Study Objectives**
  - Primary: Determine the **safety, MTD and RP2D** of CTO and TMZ
  - Secondary: Determine **pharmacokinetics (PK)** of CTO and TMZ when co-administered
  - Exploratory:
  - **Evaluate Tumor Response** in GBM and MG and confirm **proof-of–concept for a synergism between CTO and TMZ**
  - Investigate effects of CTO and TMZ on growth of tumors with **various genotypes** (MGMT +/-)
  - Investigate the effect of CTO and TMZ on gene expression (anagen hair from treated patients)
- **Study Design**
  - Combination of escalating doses of CTO up to 821mg/m^2, with fixed dose of TMZ (150mg/m^2)
  - "3+3" design, CTO administered orally at a starting dose of 219mg/m^2/day
- **Study Treatment**
  - CTO administered daily, 28-day cycle
  - TMZ administered days 1-5 of each cycle
- **Key Inclusion Criteria**
  - Histologically proven, recurrent MG
  - Measurable tumor on MRI
  - ECOG 0, 1, 2
  - Life expectancy > 8 Weeks
  - No CYP3A4 inhibitors or inducers
- **Evaluations**
  - Response: MRI every two cycles
  - Safety: Adverse events, vital signs, ECG, clinical laboratory tests, physical exams
  - Pharmacokinetics, pharmacogenomics

Table 1: Study Enrollment	N
Cohort 1 (219mg/m^2/day)	3
Cohort 2 (285mg/m^2/day)	3
Cohort 3 (370mg/m^2/day)	3
Cohort 4 (481mg/m^2/day)	3
Cohort 5 (625mg/m^2/day)	3
Cohort 6 (812mg/m^2/day)	6
Flat dose exploratory cohort (600mg/day)	6
Total Enrollment	**27**

Results

Table 2: Patient Characteristics (N=27)	
Median Age (range)	49 (28-78)
Sex	
Male	19 (70%)
Female	8 (30%)
Number of previous recurrence(s)	
1	13 (48%)
2	9 (33%)
≥3 (3-8)	5 (19%)
Leptomeningeal disease	2 (7%)
Previous systemic treatment	
Cytotoxic agents	25 (93%)
Bevacizumab / Anti-VEGF treatment	4 (15%)
Targeted therapy	4 (15%)
Immunotherapy	1 (4%)

Table 3: Histology & Molecular Features	N (%)
Histology (WHO Grade)	
Grade III	9 (33)
Grade IV	15 (56)
Unspecified malignant glioma	3 (11)
Methylated MGMT	10 (37)
Unmethylated MGMT	9 (33)
Not tested	8 (30)
IDH1/2 Status	
IDH1/2 mutant	8 (30)
IDH1/2 wild type	13 (48)
Not tested	6 (22)
1p19q Codeleted	1 (4)
1p19q Intact	14 (52)
1p19q Not tested	12 (44)

Table 4: Emergent Adverse Events Possibly, Probably or Definitely Related to CTO/TMZ

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Overall
General disorders and administrative site conditions						
Fatigue	5 (19%)	8 (30%)	0	0	0	13 (48%)
Gastrointestinal disorders						
Constipation	7 (26%)	1 (4%)	0	0	0	8 (30%)
Nausea	8 (30%)	0	0	0	0	8 (30%)
Vomiting	1 (4%)	1 (4%)	0	0	0	2 (7%)
Mucositis	0	1 (4%)	0	0	0	1 (4%)
Gastroesophageal reflux	0	1 (4%)	0	0	0	1 (4%)
Blood and lymphatic system disorders						
Thrombocytopenia	1 (4%)	1 (4%)	0	0	0	2 (7%)
Lymphocyte count decreased	0	0	1 (4%)	0	0	1 (4%)
Investigations						
Alanine aminotransferase increased	0	1 (4%)	1 (4%)	0	0	1 (4%)
Asparate aminotransferase increased	0	1 (4%)	1 (4%)	0	0	1 (4%)
Skin and subcutaneous disorders						
Dry skin	3 (11%)	0	0	0	0	3 (11%)
Rash maculo-papular	2 (7%)	0	0	0	0	2 (7%)
Rash acneiform	0	1 (4%)	0	0	0	1 (4%)
Metabolism and nutrition disorders						
Hypophosphatemia	1 (4%)	2 (7%)	0	0	0	3 (11%)
Anorexia	1 (4%)	0	0	0	0	1 (4%)
Nervous system disorders						
Dizziness	3 (11%)	0	0	0	0	3 (11%)
Dysgeusia	2 (7%)	0	0	0	0	2 (7%)
Headache	0	1 (4%)	0	0	0	1 (4%)
Tinnitus	1 (4%)	0	0	0	0	1 (4%)
Musculoskeletal and connective tissue disorders						
Myalgia	2 (7%)	0	0	0	0	2 (7%)
Bone pain	1 (4%)	0	0	0	0	1 (4%)
Eye disorders						
Blurred vision	2 (7%)	0	1 (4%)	0	0	3 (10%)
Injury, poisoning and procedural complications						
Bruising	0	1 (4%)	0	0	0	1 (4%)
Respiratory, thoracic and mediastinal disorders						
Dyspnea	1 (4%)	0	0	0	0	1 (4%)
Epistaxis	1 (4%)	0	0	0	0	1 (4%)
Infections and infestations						
Thrush	1 (4%)	0	0	0	0	1 (4%)

- N=27 pts (Tables 1, 2 and 3) were enrolled (21 pts in the dose escalation; 6 pts in an additional cohort exploring a daily flat dose of CTO 600mg, prompted by PK data indicating therapeutic concentrations above this threshold)
- **Pts were heavily pre-treated, including 4 pts failing anti-VEGF therapy and 2 with leptomeningeal disease**
- The combination was well tolerated with no DLT observed in any dose level (Table 4)
- Exploratory efficacy outcome (median follow-up of survivors: 10m)
  - Partial response (PR) = 6 (22%) including both MGMT+ and MGMT- tumors (Figure 1)
    - PRs occurred at 285-481mg/m2, and at 600mg flat dose, lasting up to 14m
  - Stable disease (SD) = 11 (41%)
  - Median OS: 10m (range 3-34); Median PFS: 3m (range 1-26)
- Evaluation of tumor tissue drug concentration in pts undergoing surgery while on treatment showed therapeutic concentrations both in areas with and without disruption of the blood-brain barrier (Table 5). CSF concentrations were lower than brain tumor concentrations.

Figure 1 MRI in Responders: Baseline (1) and at response (2); (A-B: MGMT-; C: MGMT+; D-F: MGMT unknown)

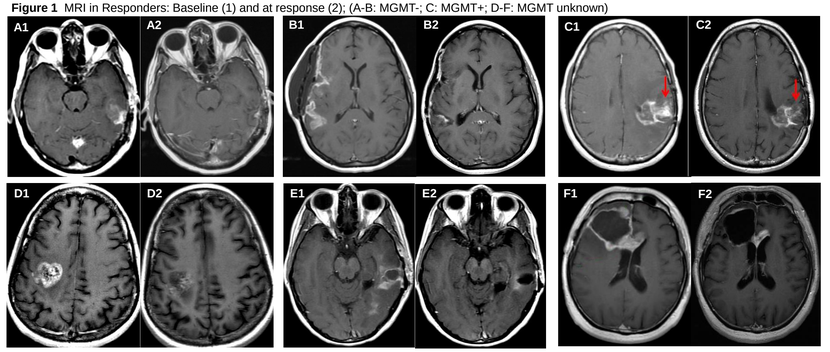

Table 5 Levels of active metabolite (CAI) in plasma, tumor tissue, and CSF obtained in pts who underwent surgery or lumbar puncture during the study

Patient	CTO Dose	CSF (ng/ml)	Tumor (ng/g) Enhancing	Tumor (ng/g) Non-enhancing
004-64	625 mg/m^2/day	31.9	2285	1705
004-71	812.5 mg/m^2/day			6200
004-70	812.5 mg/m^2/day	22.1		
004-89	600 mg/day		1020	1185

Conclusions

- CTO in combination with TMZ is safe and well tolerated.
- CTO crosses the blood-brain barrier and achieves therapeutic concentrations in the brain and tumor
- The MAD was 812 mg/m2/day, with no DLTs observed. Additional PK evaluations are ongoing to confirm the 600 mg flat dose as the RP2D
- Responses were seen across different dose levels. Durable PRs were observed in both MGMT+ and MGMT- tumors, indicating that CTO induced sensitivity to TMZ. Given clinical signals of activity and favorable toxicity profile, Phase II studies are planned.

OmuroA@mkscc.org