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A PHASE I STUDY OF CARBOXYAMIDOTRIAZOLE OROTATE (CTO) IN TREATMENT OF ADVANCED SOLID TUMORS

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BACKGROUND

CTO is the orotic acid salt of Carboxyamidotriazole (CAI) (Figure 1), which is an inhibitor of calcium dependent intracellular and extracellular signal transduction pathways, and has anti-proliferative, anti-angiogenic, and anti-invasive properties (Kohn, 1997; Berlin, 1997).

Several Phase I, II, and III clinical trials have been described on CAI (L-651,582) but CAI's development was terminated in 2008 because of its poor bioavailability, serious neurotoxicity profile and lack of efficacy.

STUDY OBJECTIVES

Primary – Arm A
- Determination of Safety and Tolerability of CTO administration to patients with advanced or metastatic solid tumors
- To determine the Maximum Tolerated Dose (MTD) of CTO

Primary – Arm B
- Determination of Safety and Tolerability of CTO+Temodar® (TMZ) administration to patients with glioblastoma and other malignant gliomas
- To determine the Maximum Tolerated Dose (MTD) of CTO+TMZ

Secondary
- To determine tumor response in solid tumor patients treated with CTO alone (Arm A)
- To determine tumor response in patients with GBM and malignant gliomas in patients treated with CTO and TMZ
- To determine the pharmacokinetics of CTO and TMZ

Exploratory – Arm A & B
- Investigate the effect of CTO on tumor growth based on tumor genotype

STUDY DESIGN

This is a multi-arm, multi-center dose escalation study of CTO with and without TMZ. (Figure 3)

Arm A
- This arm has a "3+3" design with a CTO Starting Dose of 50mg/m^2, with dose escalations of 30-100% depending upon the pharmacokinetics of the previous cohort's patients

Arm B
- This arm has a "3+3" design with a CTO Starting Dose of 219mg/m^2 combined with a fixed TMZ dose of 150mg/m^2 (Dose determined in Arm A)

Dose Limiting Criteria
- ≥ Grade 3 Nausea/Vomiting despite maximal antiemetic therapy
- ≥ Grade 3 Diarrhea despite maximal antidiarrheal therapy
- Any Other Grade 3/4 non-hematologic toxicity
- Any Grade 4 Neutropenia >5 Days, or Grade 3 neutropenia w/fever of any duration or where significant sepsis results
- Grade 4 Thrombocytopenia

INVESTIGATIONAL PRODUCT

CAI inhibits calcium-dependent signal transduction via receptor-operated and voltage-gated calcium channels. The subsequent decrease in influx of calcium and intracellular calcium leads to diminished cell proliferation and protein phosphorylation. (Cole, 1999)

The orotate salt of CAI (CTO) has increased bioavailability, faster clearance and reduced toxicity compared to unaltered CAI. Orotic acid is a naturally occurring substance in cow's milk. CTO has demonstrated the ability to inhibit multiple tyrosine kinase signaling pathways including Akt, ERK and Bcr-Abl (Corrado, 2012). Mice bearing human glioblastoma xenograft tumors were treated with CTO and Temodar® resulting in supra-additive anti-tumor activity compared to CTO or Temodar® alone (Figure 2). Additionally, CTO has been demonstrated to cross the blood brain barrier in mouse models (Karmali, 2011).

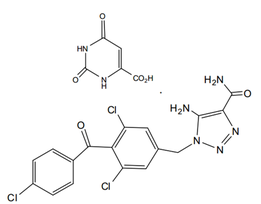


Figure 1: Structural Formula of CTO (CAI + Orotic Acid)

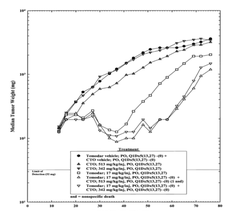


Figure 2: Response of SC U251 Human CNS Tumor to Combination Treatment with TMZ and CTO

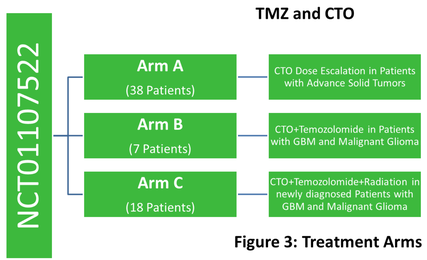


Figure 3: Treatment Arms

References:
Berlin, J., et al, *J. Clin Oncol* 1997, 15: 781-789
Cole, K., Kohn, E. *Canc & Mets Rev*. 1994, 13:31-44
Corrado, C., et al, *PLos ONE* 2012, 7: 1-13
Karmali, RA., et al, *Cancer Therapy* 2011, 8: 71-80
Kohn E.C., et al, *J. Clin Oncol* 1997, 15: 1985-1993.

METHODS

Key Inclusion Criteria
- Histologically-confirmed solid tumors that are advanced or metastatic, and refractory after standard therapy, or for which there is no standard therapy. (Arm A)
- Histologically proven malignant glioblastoma multiform or other recurrent malignant glioma. (Arm B)
- ECOG performance status of 0, 1, or 2.
- Patients must have measurable disease as defined by RECIST 1.1 (Arm A), or measurable disease on an enhanced MRI (Arm B).

Arm A
- CTO Administered on C1D1 and C1D8-36.
- PK on C1D1-8, 15, 22,2 9, 36.

Arm B
- CTO Administered on C1D1-28, TMZ Administered C1D1-5
- PK on C1D1, 5, 29.

RESULTS

Study Enrollment (45 Patients to date)	
Arm A	
Cohort 1 (50mg/m^2), n= 3	Cohort 5 (219mg/m^2), n= 4
Cohort 2 (75mg/m^2), n= 3	Cohort 6 (285mg/m^2), n= 3
Cohort 3 (112.5mg/m^2), n= 4	Cohort 7 (427mg/m^2), n= 3
Cohort 4 (146mg/m^2), n= 10	Cohort 8 (555mg/m^2), n= 8
Arm B	
Cohort 1 (219mg/m^2), n= 4	Cohort 2 (285mg/m^2), n= 3

Characteristics	N	N (%)
Age (Years)	45	
Median		61
Range		24-85
Sex	45	
Male		23 (51%)
Female		22 (49%)
Tumor Type	45	
Gastrointestinal		16 (36%)
Brain		7 (16%)
Pulmonary		5 (11%)
Ovarian		5 (11%)
Unknown Primary		3 (7%)
Integumentary		2 (4%)
Bone/Connective Tissue		2 (4%)
Pancreatic		2 (4%)
Head & Neck		1 (2%)
Endocrine		1 (2%)
Renal		1 (2%)

Table 1: Patient Demographics

Pharmacokinetic Sample Collection
- Serial Sampling 0-48 hours post single-dose of CTO, and at steady state following 27 days of consecutive CTO administration. (Figure 3)

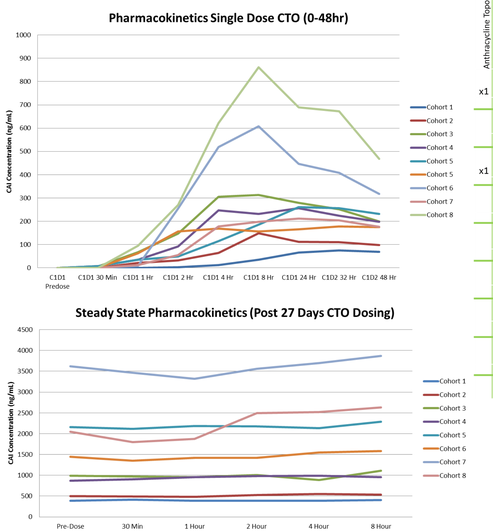


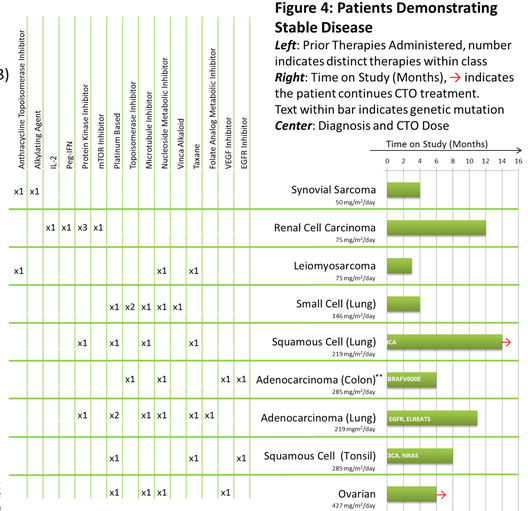
Figure 5: Drug Concentration Over Time

Treatment-Emergent Adverse Event	N(%)
Safety evaluable patients	37 (100%)
Number of patients with any TEAEs	33 (89.2%)
Fatigue	21 (56.8%)
Nausea	16 (43.2%)
Vomiting NOS	15 (40.5%)
Anorexia	8 (21.6%)
Diarrhea NOS	7 (18.9%)
Dizziness	6 (16.2%)
Abdominal Pain NOS	6 (16.2%)
Hypomagnesaemia	5 (13.5%)
Constipation	4 (10.8%)
Hyponatremia	5 (13.5%)
Cough	5 (13.2%)
Chest Pain	4 (10.8%)
Weakness	4 (10.8%)
Abdominal Distention	4 (10.8%)
Dyspnea NOS	4 (10.8%)
Confusion	4 (10.8%)

Table 2: TEAEs Occurring in >10% of Subjects

Figure 4: Patients Demonstrating Stable Disease

Left: Prior Therapies Administered, number indicates distinct therapies within class
Right: Time on Study (Months), → indicates the patient continues CTO treatment.
Text within bar indicates genetic mutation
Center: Diagnosis and CTO Dose



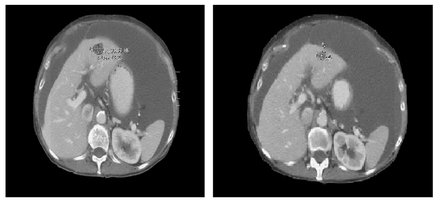


Figure 6: CT Images of Patient 002-25 (BRAFV600E, KRASwt)**
Demonstrating a 15% decrease in longest diameter. Baseline **(L)**; Cycle 4 **(R)**

CONCLUSIONS

- CTO has better bioavailability than CAI, is safe and tolerable and has yet to reach MTD at up to 555mg/m^2/day.
- Steady state plasma levels of CAI up to 4250ng/ml were observed at 555mg/m^2/day dosing (after 15 days).
- Nine patients pretreated with different targeted and non-targeted drugs had *refractory* tumors which responded to CTO (doses 75mg/m^2/day through 427mg/m^2/day) and achieved stable disease for different periods (3-14+ months). Four pretreated tumors were found to have different genomic mutations (PI3KCA, EGFR multiple, BRAFV600 & NRAS) consistent with CTO's suggested mechanism of action to inhibit multiple tyrosine kinase signaling pathways.