Phase IB Trial of Carboplatinomide 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-VGAT-dependent calcium signaling that simultaneously modulates several receptor-mediated calcium-dependent signaling pathways, including EGFR, MEK, NFκB, RAS, HBC, HSP90, WNT,-catenin, Akt, ERK, VEGF and Bcl-Abl. (Kohn, 1997, Berlin, 1997, Corrado 2012; Karmali, 2013)
- A single-agent phase 1 trial determined the maximum tolerated dose (MTD) at 42 mg/m2, with a safe toxicity profile (ASCO 2013; Taylor, 2015)
- A phase II dose escalation of CTO with temozolomide (TMZ) for recurrent malignant glioma (MGB) found therapeutic brain tumor 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 TMZ in newly diagnosed GBM and other MGB
Secondary/Objective: Tumor response according (Macnoldrid criteria)
Determine Pts 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 mg /m2/day), n= 3 481 mg /m2/day), n= 3
dose escalation at 481 mg /m2/day). No toxic deaths observed

Treatment
- A total of 15 pts were enrolled across multiple GBM molecular profiles (next generation sequencing done in 10 of 15 patients- Table 2)
- ChemRT was well tolerated at CTO doses of 219-481 mg/m2 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).

Fig1: Pharmacokinetics data confirmed therapeutic levels starting at 219 mg/m2. Shown below: Dose Proportionality of AUC0-8 (A), AUC2-4 (B) and Cmax (C) following multiple-dose administration of CTO with quadratic nonlinearity regression line

Results
- Table 2: Patient characteristics (N=15)
- Table 3: Dose CTO mg/m2/day Plasma volume (ml/kg) Plasma level (ng/ml) 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.

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/m2/day and RP2D is 370 mg/m2/day.
- Exploratory efficacy evaluation suggests highly promising PFS and OS across multiple phenotypes; a randomized phase II study is planned.

Fig 2: Durable Radiographic Response; Axial T1 post contrast MRI at diagnosis and after 21 dose cycles demonstrating near complete resolution of enhancing mass crossing the corpus callosum. This patient received chem-RT with TMZ and CTO 370 mg/m2/day for 12 adjuvant cycles and then went on to single agent CTO, remaining progression free with a PFS of 90.