Phase II/I Study of Dianhydrogalactitol in Patients with Recurrent Malignant Glioma Multiforme (GBM)

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ABSTRACT 4CT21

- Dianhydrogalactitol (GBM) is the most common and deadly form of human brain cancer. Median survival for patients with recurrent GBM is 4-7 months. Front-line systemic therapy is temozolomide, but resistance due to O6-methylguanine-DNA methyltransferase (MGMT) activity is implicated in poor prognosis. Dianhydrogalactitol (VAL-083) is a structurally unique inulinoid DNA alkylating agent that crosses the blood-brain barrier and accumulates in brain tumor tissue. In recent in vitro studies, VAL-083 overcomes resistance to MGMT and demonstrated cytotoxic activity against glioblastoma cell lines and primary tumor xenografts. Previous studies showed endothelial cell toxicity, but in vitro and in vivo studies demonstrated that VAL-083 does not inhibit angiogenesis.

SAFETY AND TOLERABILITY

The purpose of this Phase II/I, open-label, single-arm study dose escalation study (standard 3×3 design) is to determine the safety and the maximal tolerated dose (MTD) of VAL-083 in patients with recurrent malignant gliomas for advanced treatment of refractory GBM. Patients have been enrolled at doses up to 50 mg/m2/day for 5 days every 21 days. The optimized dosing regimen in this phase III trial will utilize a daily dose for three days every three weeks for at least 3 cycles. To determine an appropriate dose for advancement into registration trials as a potential new therapy for the treatment of refractory GBM.

RESULTS AND OBJECTIVES OF THE STUDY (study ongoing):

Using an optimized dosing regimen, we have achieved significantly higher doses in comparison to the NCI regimen before encountering dose limiting toxicity (DLT) using a dosing regimen of VAL-083 given 30 mg/m2/day for three days every 21 days. As anticipated from the dose, the low toxicity of VAL-083 appears to be thrombocytopenia (NCI-CTAE Grade 4 thrombocytopenia: 2/13, 15.4%) with NADIR occurring between day 14 and day 21, with rapid and spontaneous recovery of platelet counts (Table 3 and Fig 2).

BACKGROUND:

VAL-083 (dianhydrogalactitol) is a bifunctional alkylating agent causing interstrand DNA-crosslinks at the N-Terminus of guanine via a mechanism that offers distinct advantages over other alkylating agents used in the treatment of GBM. The MGMT inhibitor, temozolomide (TMZ), has been widely accepted as the standard of care treatment of GBM. However, the management of recurrent GBM is challenging due to aggressive tumor regrowth and resistance to salvage treatments. Inactive or down-regulated MGMT in GBM is <6 months. Frontline therapy of VAL-083 overcame resistance to TMZ in GBM cell lines SF188 (pediatric), U251 (adult), and T98G (human GBM). These observations are consistent with prior reports of VAL-083 in GBM support the potential for pharmacodynamic and pharmacokinetic studies to determine an appropriate dose for advancement into registration trials as a potential new therapy for the treatment of refractory GBM.

We hypothesized that improvement in management of GBM with VAL-083 offers the potential to extend patient survival and improve quality of life. Historically, toxic effects of VAL-083 included myelosuppression (thrombocytopenia and neutropenia), nausea, vomiting, fatigue, and mild to moderate anemia. Neutropenia was noted to occur spontaneously without concomitant treatment. Prior to this, other treatment-related toxicities have been mild to moderate and included two 1-grade hepatotoxicity and one grade 2 hepatotoxicity. These three patients had a response (stable disease or partial response) and interrupted clinical signs (maximum response of 8 weeks). Pharmacokinetic analysis showed dose-dependent linear systemic exposure with a short plasma half-life. Cross ranged from 730–1300 ng/mL, 1.2–7.1 µg/mL at 48 h. Compared to historical trials, the present regimen delivers substantially more drug than previous valricosine dosing and results in higher dose intensity of 25 mg/m2/kg in combination with radiation.

The detailed summary of thrombocytopenia observed in cohort 8 are presented in Table 3 and Figure 2, respectively. Observed thrombocytopenia in GBM supports the potential for pharmacodynamic and pharmacokinetic studies to determine an appropriate dose for advancement into registration trials as a potential new therapy for the treatment of refractory GBM. Patients have been enrolled at doses up to 50 mg/m2/day for 5 days every 21 days. The optimized dosing regimen in this phase III trial will utilize a daily dose for three days every three weeks for at least 3 cycles. To determine an appropriate dose for advancement into registration trials as a potential new therapy for the treatment of refractory GBM.

ANTICANCER ACTIVITY:

VAL-083 demonstrated promising results in the treatment of both newly-diagnosed and recurrent GBM in historical NCI-sponsored clinical trials with median overall survival equal or superior to other alkylating agents approved for the treatment of GBM. The goal of the current trial is to advance this promising agent into dosing regimens of VAL-083 for advanced treatment of refractory GBM.

Patients enrolled have recurrent GBM that has failed to respond to prior therapy. Cycle 1 toxicity is measured for MTD determination. Tumor volume is measured via RANO criteria prior to every 21-28 days of treatment cycle and only patients exhibiting stable disease or tumor regression after one cycle of treatment are allowed to stay on study drug. During the dose-escalation phase, toxicities have been observed on MTD (Fig. 1). 3 patients exhibited intra-tumoral hemorrhage, one patient exhibited an expression (stable disease or partial response) reported improved clinical signs with VAL-083 treatment, hence his cycle of treatment was excluded and data obtained from the trial were re-reviewed. These interim results support the continued development of VAL-083 as a potential treatment to extend patient survival and improve quality of life.

PHARMACOLOGY:

Pharmacokinetic analyses show dose-dependent linear systemic exposure with a short plasma half-life. Cross ranged from 730–1300 ng/mL, 1.2–7.1 µg/mL at 48 h. In vivo studies indicate MGMT concentrations of DAE are effective against various glioma cell lines. Fig. 3 plots observed RNA levels of MGMT compared to the data where literature was performed at MGMT (Eagan et al. 1982). Fig. 4 shows the Dose-AML relationship. Extropeptization of CNS exposure based on information in the published literature, we calculated that observed plasma concentrations obtained from platelet counts to be derived from CNS tissue concentrations effective against glioma cell lines in vitro (Table 4).

CONCLUSIONS & NEXT STEPS:

- VAL-083 is a cytotoxic alkylating agent with a unique bi-functional mechanism that overcomes MGMT-related tumor resistance in vitro
- VAL-083 can be dosed more aggressively than in historical clinical studies, potentially leading to improved patient outcomes
- Pharmacokinetic data suggest significant CNS exposure concentrations sufficient for cytotoxic anti-tumor effects
- Based on historical and recent data, VAL-083 shows promise as both single-agent therapy for new onset GBM who fail or are unlikely to respond to current standard-of-care.
- Observation of Grade 3 and Grade 4 thrombocytopenia at the current (50mg/m2) dose cohort suggest determination of MTD for advancement to registration-directed clinical trials is imminent.

Table 1: Historical clinical data of TMZ and VAL-083 in GBM support the potential for comparable or enhanced survival and improved safety compared to other alkylating agents such as TMZ in intracranial-based therapy.

Table 2: Summary of pharmacokinetic studies in GBM showing VAL-083’s effective plasma concentrations in humans.

Table 3: Summary of toxicity observed in GBM patients treated with VAL-083 (n=5).

Table 4: Summary of pharmacokinetic studies in GBM showing VAL-083’s effective plasma concentrations in humans.

Fig. 1: In-vitro activity of 1µM and 10µM TMZ resistance in GBM cell lines SF188, SA81 (adult), T98G (human GBM). MGMT is considered to be resistant to VAL-083 in patients with GBM.

Fig. 2: Observed Relative Counts in Cohort 3 (50 µg/m2).

Fig. 3: Example of observations on platelet count before (Mar 4, 2014) and after (May 7) 2 cycles of VAL-083 treatment.

Fig. 4: Dose-AML relationship.