

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

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ABSTRACT # CT217:

Glioblastoma multiforme (GBM) is the most common and deadly form of human brain cancer. Median survival for patients with recurrent GBM is <6 months. Front-line systemic therapy is temozolomide, but resistance due to O⁶-methylguanine-DNA-methyltransferase (MGMT) activity is implicated in poor prognoses. Dianhydrogalactitol (VAL-083) is a structurally unique bi-functional DNA alkylating agent that crosses the blood-brain barrier and accumulates in brain tumor tissue. In recent *in vitro* studies, VAL-083 overcame resistance to MGMT and demonstrated cytotoxic activity against GBM cell lines, as well as GBM cancer stem cells, and was shown to act as a radiosensitizer. Previous clinical trials suggest that VAL-083 has activity against a range of tumors, including GBM. Historical NCI-sponsored studies in GBM achieved promising results with limited toxicity using a dosing regimen of 25mg/m²/day for five days every five weeks. The optimized dosing regimen in this phase I/II trial utilizes a daily dose for three days every three weeks. The goal of the current clinical trial is to determine an appropriate dose for advancement into registration trials as a potential new therapy for the treatment of refractory GBM. **Method:** Open-label, single-arm Phase I/II dose-escalation study in patients with histologically-confirmed initial diagnosis of primary WHO Grade IV malignant glioma (glioblastoma). Patients enrolled have previously been treated with surgery and/or radiation, if appropriate, and must have failed both bevacizumab and temozolomide, unless contraindicated. The study utilizes a 3+3 dose-escalation design. Patients receive VAL-083 IV on days 1, 2, and 3 of a 21-day cycle. Tumor response is assessed according to RANO criteria prior to every other 21-day treatment cycle, and patients exhibiting stable disease or tumor regression are allowed to remain on study drug. **Results:** 37 patients have been enrolled across 8 dose cohorts ranging from 1.5 to 50mg/m²/d. One dose limiting toxicity consisting of grade 4 thrombocytopenia was observed at dose level 8 (50mg/m²/d). The DLT-related symptoms resolved rapidly and spontaneously without concomitant treatment. Prior to this, other treatment related toxicities have been mild to moderate and included two grade 1 lymphopenias and one grade 1 thrombocytopenia. Maximum tolerated dose (MTD) will be determined based on 3+3 design. Three patients had a response (stable disease or partial response) reporting improved clinical signs (maximum response of 84 wks). Pharmacokinetic analyses show dose-dependent linear systemic exposure with a short plasma 1-2h terminal half-life; C_{max} ranged from 739–1130 ng/mL (5.1–7.7 μM) at 40mg/m²/d. Compared to historical trials, the present regimen delivers substantially more drug by C_{max} and dose intensity. A dose intensity of 25 mg/m²/wk in combination with radiation was previously shown superior to radiation alone against GBM; a dose intensity of 50 mg/m²/wk is achieved in the current trial. **ClinicalTrials.gov Identifier** NCT01478178.

BACKGROUND:

VAL-083 (*dianhydrogalactitol*) is a bifunctional alkylating agent causing interstrand DNA crosslinks at the N⁷ position of guanine via a mechanism that differs from other alkylators used in the treatment of GBM^{1,2,3}. In prior clinical studies sponsored by the US National Cancer Institutes, VAL-083 exhibited clinical activity against a number of tumor-types in a number of cancers including lung, brain, cervical, ovarian and hematologic malignancies. VAL-083 is approved in China for the treatment of chronic myelogenous leukemia and lung cancer and has received orphan drug designation in Europe and the U.S. for the treatment of gliomas.

We have previously demonstrated that VAL-083 is active against temozolomide-resistant cancer stem cells and retains cytotoxic activity independent of the repair enzyme MGMT (O⁶-methylguanine methyltransferase) *in vitro*⁴. MGMT is correlated with temozolomide resistance and poor GBM patient outcomes.

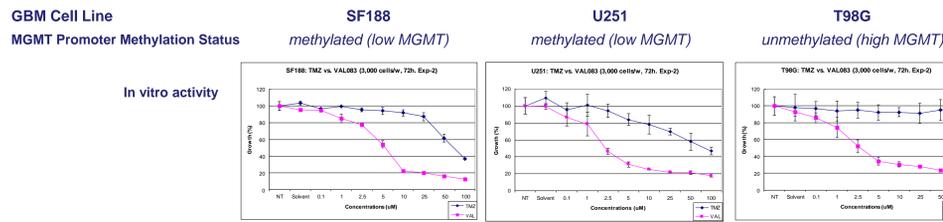


Fig 1. *In vitro* activity of VAL-083 vs. TMZ resistance in GBM cell lines SF188 (pediatric), U251 (adult), and T98G (adult) as impacted by expression of MGMT repair enzyme⁵

Historical NCI-sponsored studies achieved promising results in patients with newly diagnosed and recurrent GBM using a dosing regimen of VAL-083 given 25 mg/m²/day for five days every five weeks⁶. These data suggest comparable or enhanced survival and improved safety compared to other alkylating agents such as TMZ or nitrosourea-based therapy.

Table 1. Historical clinical data of TMZ or VAL-083 in GBM support the potential for comparable or enhanced survival similar to standard-of-care chemotherapy

Chemotherapeutic Agent	MGMT Promoter Status	XRT		p-value
		Alone	+ Chemotherapy	
median survival (mo.)				
LOMUSTINE ⁽⁶⁾	n/a	n/a	11.9	n/a
CARMUSTINE ⁽⁶⁾	n/a	n/a	9.2 - 11.5	n/a
SEMUSTINE ⁽⁶⁾	n/a	n/a	8.0	n/a
TMZ ⁽⁷⁾	Methylated (low MGMT expression)	15.3	21.7	0.007*
	Unmethylated (high MGMT expression)	11.8	12.7	0.06
VAL-083 ⁽⁸⁾	n/a		16.8	0.02*

*statistically significant improvement p-value by log-rank test

Historically, toxic effects of VAL-083 were noted on white blood cell (WBC) and platelet counts. For example, Eagan et al (1979) observed nadir of 2,100/μL (lymphopenia) and 88,000/μL (thrombocytopenia) in patients with newly diagnosed and recurrent GBM using a dosing regimen of VAL-083 given 25 mg/m²/day for five days every five weeks⁹. In a separate study, a dose of 40mg/m²/day VAL-083 for five days resulted in a median platelet nadir of 31,000/μL and WBC nadir of 2,300/μL⁹. In general, nadir occurred within three weeks and returned to normal within 7 days. Anemia, nausea and vomiting were usually mild to moderate. No renal, hepatic, central nervous system, cardiac, or pulmonary toxicity was identified.

We hypothesized that improvement in management of myelosuppression in the modern era would allow for more aggressive dosing and potentially improved outcomes for GBM patients in comparison to already-promising results from historical NCI-sponsored clinical trials.

Based on its differentiated cytotoxic mechanism, we further believe that VAL-083 may provide a viable treatment option and the potential to surpass standard-of-care for patients suffering from GBM, particularly those GBM patients who fail or are unlikely to respond to the current standard-of-care.

References:

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RESULTS AND OBSERVATIONS TO DATE (study ongoing):

SAFETY AND TOLERABILITY

The purpose of this Phase I/II, open-label, single-arm study dose escalation study (standard 3x3 design) is to determine the safety and the maximal tolerated dose (MTD) of VAL-083 in patients with recurrent malignant glioma for advancement into future registration-directed clinical trials. The goal is to maximizing tumor exposure to VAL-083 while limiting systemic toxicity, and to explore pharmacokinetic (PK) properties and tumor responses to treatment. To date, 19 male and 11 female subjects with GBM (mean age = 52 +/- 12.6) have been enrolled at doses up to 50mg/m². Seven additional subjects with CNS metastases were enrolled at lower doses; however, enrollment at doses above 5mg/m² have been limited to patients with GBM. The determination of MTD will be based on analysis of tolerance data from the first cycle of therapy in each dose group at 35 days following initial treatment. Patients exhibiting stable disease or tumor regression following one cycle of treatment are permitted to remain on study drug at the dose in which they were first enrolled.

DOSE & STUDY	Single Dose	Acute Regimen (single cycle)	Comparative Dose (@ 35 days)	Dose Intensity (dose per week)	Status
NCI GBM (Eagan) ⁹ daily x 5 q 5wks (cycle = 35 days)	25 mg/m ²	X 5 days = 125 mg/m ²	125 mg/m ²	25mg/m ² /wk	Historical Regimen
DelMar VAL-083 daily x 3 q 3wks (cycle = 21 days)	30 mg/m ²	X 3 days =	90 mg/m ²	180 mg/m ²	No DLT
	40 mg/m ²		120 mg/m ²	240 mg/m ²	No DLT
	50 mg/m ²		150 mg/m ²	300 mg/m ²	50mg/m ² /wk

Based on the observation of one DLT in three patients, enrollment of the 50 mg/m² cohort was expanded to six patients. If DLT occurs in any additional patients in the 50 mg/m² cohort, we would then propose the highest previous safe dose – 40 mg/m² – as the MTD for advancement to registration-directed trials. If no further DLT is observed, the protocol currently allows dosing up to 60 mg/m². However, if continued strong trends toward DLT are observed it is possible that we may cease dose-escalation and propose 50 mg/m² as the MTD. An overview of hematologic toxicities observed to date and a detailed summary of thrombocytopenia observed in cohort 8 are presented in Table 3 and Figure 2, respectively. Observed thrombocytopenia has resolved rapidly and spontaneously, as predicted based on prior NCI-sponsored clinical studies.

The final decision on the dose chosen for advancement to registration directed studies will be determined by the safety and tolerability of our modernized dosing regimen as we achieve an MTD. Once MTD is determined, we plan to expand enrollment at that dose by an additional 14 patients in accordance with the protocol. During this period, we plan to request a guidance meeting with the FDA to discuss our proposed registration trial design.

PHARMACOKINETICS:

Pharmacokinetic analyses show dose-dependent linear systemic exposure with a short plasma 1-2 h terminal half-life; C_{max} at the highest dose tested (cohort 7, 40 mg/m²) ranged from 739 to 1130 ng/mL (5.1 to 7.7 μM). *In vitro* studies indicate μM concentrations of DAG are effective against various glioma cell lines. Fig. 3 plots observed PK results by cohort, and compares the data to the literature where patients were dosed at 50 mg/m² (Eagan et al. 1982).¹¹ Fig. 4 shows the Dose-AUC relationship.

By extrapolating CNS exposure based on information in the published literature, we can calculate that observed plasma concentrations obtained to date are predicted to exceed in CNS tissue concentrations effective against glioma cell lines *in vitro* (Table 4).

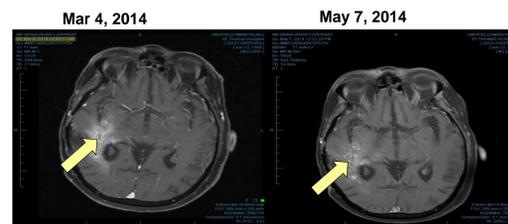
ANTI-TUMOR ACTIVITY:

VAL-083 demonstrated promising results in the treatment of both newly-diagnosed and refractory 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 establish the maximum tolerated dose (MTD) of our modernized dosing regimen for advancement into registration directed trials as a potential new therapy for the 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 other 21-day treatment cycle and only patients exhibiting stable disease or tumor regression after one cycle of treatment are allowed to remain on study drug. During the dose-escalation phase, observations have been reported on MRI (Fig. 5) and three patients exhibiting a response (stable disease or partial response) reported improved clinical signs with a maximum response of 28 cycles (84 weeks) prior to discontinuing due to adverse events unrelated to study drug. These interim results support the continued development of VAL-083 as a potential treatment to extend patient survival and improve quality of life.

Fig 5: Example of observations on MRI scans of patient #26 before (Mar-4), and after (May 7) 2 cycles of VAL-083 treatment. Thick confluent regions of abnormal enhancement have diminished, now appearing more heterogeneous.



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 50 mg/m²/day for three days every three weeks (see Table 2). As anticipated from the literature, the dose limiting toxicity of VAL-083 appears to be thrombocytopenia (NCI-CTAE Grade 4 thrombocytopenia: platelets <25,000/μL) with NADIR occurring between day 14 and day 21, with rapid and spontaneous recovery of platelet counts (Table 3 and Fig. 2).

Cohort	Dose & hematologic toxicity	Grade 3	Grade 4	Grade 5
1 – 6 (n=x)	up to 30 mg/m ²			
	LYMPHOPENIA	0	0	0
	THROMBOCYTOPENIA	0	0	0
7 (n=3)	40 mg/m ²			
	LYMPHOPENIA	1	0	0
	THROMBOCYTOPENIA	0	0	0
8 (n=6) observations to date	50 mg/m ²			
	LYMPHOPENIA	1	0	0
	THROMBOCYTOPENIA	3	1	0

Fig. 2 Observed Platelet Counts in Cohort 8 (50 mg/m²)

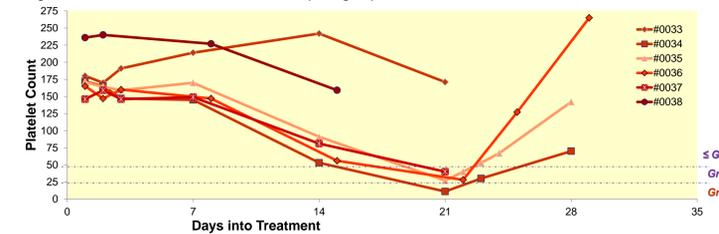


Fig 3. PK by dose cohort & published literature

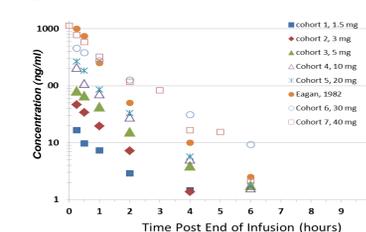


Fig 4. Dose-AUC relationship

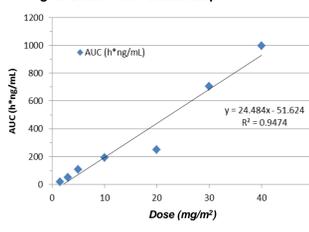


Table 4. Estimated Tumor Concentration in Human Brain Exceeds *in vitro* IC₅₀

Dose and Dosing Day of Each Cycle Current Regimen	Plasma C _{max} (μg/mL) ¹	Estimated Maximum Tumor Concentration in Brain ^{2,3}		IC ₅₀ in GBM Cell Lines
		(μg/g tissue)	μM ⁴	
40mg/m ² Day-1	0.781	0.344	2.36	2.5-5.0
40mg/m ² Day-2	0.781	0.503	3.45	2.5-5.0
40mg/m ² Day-3	0.781	0.563	3.86	2.5-5.0

- From study DLM-10-001, cohort #7; PK was conducted only on Day 1, given the short t-1/2 of ~1h C_{max} is assumed to be same for Day 2 & 3.
- Percent of plasma drug concentration in brain tumor = 44%, Eckhardt, 1977¹⁰
- Half-life of drug in human brain tissue = 20h, Eckhardt, 1977¹⁰

*Volume of 1 g tissue assumed to be 1 mL

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 at concentrations sufficient for cytotoxic anti-tumor effects
- Based on historical and recent data, VAL-083 shows promise as potential therapy for GBM patients 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.