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

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Abstract # AT-53: Median survival for patients with recurrent GBM is <6 months. Front-line systemic therapy is temozolomide but resistance due to O^6-methylguanine-DNA-methyltransferase (MGMT) activity is implicated in poor outcomes. Dianhydrogalactitol (VAL-083) is a structurally unique bi-functional DNA alkylating agent that accumulates in brain tumor tissue. In *in vitro* studies, VAL-083 demonstrated activity in pediatric and adult GBM cell lines, as well as GBM cancer stem cells[1]. Notably, VAL-083 overcomes resistance to MGMT *in vitro.* Previous clinical studies suggest that VAL-083 has anti-tumor activity against a range of tumors, including GBM. In light of extensive safety data from clinical trials and promising efficacy in CNS tumors, we initiated a new clinical study to establish the maximum tolerated dose (MTD) and identify a dose and dosing regimen for future efficacy trials in GBM. Early in the development of VAL-083, a cumulative IV dose of 125 mg/m^2 delivered in a 35 day cycle in combination with radiation was shown superior to radiation alone in brain cancer[2].

In the present study, the cumulative dose in the same cycle time ranges from 9 mg/m^2 (cohort 1) to 300 mg/m^2 (cohort 8). Seven dose cohorts have completed the trial with no drug-related serious adverse events: MTD was not yet reached. Enrollment for cohort 8 (33 day cumulative dose: 300 mg/m^2) has been initiated and higher doses may be explored; the results will determine the design of the safety and efficacy registration trial.

Method: Open-label, single-arm Phase I/II dose-escalation study in patients with histologically-confirmed initial diagnosis of malignant GBM. 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. GBM patients previously treated with surgery and/or radiation, if appropriate, must have failed both bevacizumab and temozolomide, unless contraindicated.

ClinicalTrials.gov Identifier: NCT01478178

BACKGROUND:

GBM is the most common and deadly form of human brain cancer. Temozolomide (TMZ) in combination with radiotherapy (XRT) followed by maintenance therapy with TMZ alone is standard of care in the treatment of newly diagnosed GBM. The anti-tumor mechanism of TMZ is mainly through monofunctional alkylation of the O^6 position of guanine. MGMT (O^6-methylguanine methyltransferase) is a DNA-repair enzyme that removes alkyl groups for the O^6 position of guanine. High levels of MGMT are ascribed to an unmethylated MGMT promoter and correlated with poor patient outcomes and failure of temozolomide therapy.

VAL-083 *(dianhydrogalactitol)* is a bifunctional alkylating agent causing interstrand DNA crosslinks at the N^7position of guanine[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 retains cytotoxic activity independent of MGMT expression *in vitro*. Historical clinical data further suggest comparable or enhanced survival and improved safety compared to TMZ. Based on its differentiated cytotoxic mechanism, we believe that VAL-083 may provide a viable treatment option for patients suffering from GBM who fail or are unlikely to respond to the current standard-of-care.

Table 1. **Historical clinical data with VAL-083 support the potential for comparable or enhanced survival similar to standard chemotherapy**

Chemotherapeutic Agent	MGMT Promoter Status	XRT Alone (median survival (mo.))	XRT + Chemotherapy (median survival (mo.))	p-value
TMZ *Hegi etal (2005)*	Methylated *(low MGMT expression)*	15.3	21.7	0.007*
	Unmethylated *(high MGMT expression)*	11.8	12.7	0.06
VAL-083 *Eagan etal (1977)*	n/a	8.8	16.8	0.02*

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

Fig 1. **Kaplan-Meier OS Estimates following TMZ by MGMT Status** *(Heigi,etal)*

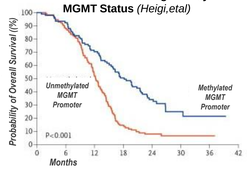


Fig 2. In vitro activity of VAL-083 vs.TMZ resistance in GBM cell lines SF188 (pediatric), U251 (adult), and T98G (adult) as impacted by expression of MGMT repair enzyme

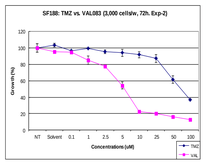
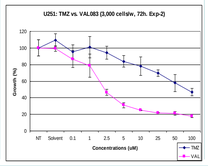
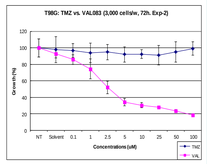
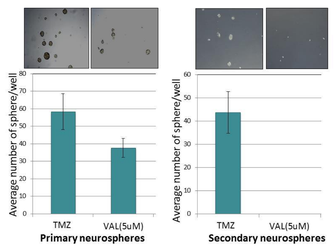
GBM Cell Line	SF188	U251	T98G
MGMT Promoter Methylation Status	*methylated*	*methylated*	*unmethylated*
In vitro activity			

Fig 3. VAL-083 inhibits the growth of Brain Tumor Initiating cells (BTIC) (BT74, GBM4 and GBM8) by 80-100% in neurosphere growth assays, with minimal effect on normal human neural stem cells. Temozolomide is ineffective against BTICs.



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2. Eagan R.T, *et at.* Cancer Treat Rep. 1982; 66 (2), 283-7.
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Results and Observations to date (study ongoing):

To date, 13 male and 10 female subjects with GBM have completed safety analysis at doses up to 40mg/m^2. Seven additional subjects with CNS metastases were enrolled at lower doses; however, enrollment at doses above 5mg/m^2 have been limited to GBM.

Table 2. **Quantitative Demographic Summary of GBM Patients Completing Study to Date**

Parameter	Mean ± SD	Median	Range
Age	53.4 ± 12.0	57.2	22.6 - 69.0
Height (cm)	171.2 ± 11.5	175.3	139.7 - 188.6
Weight (kg)	80.7 ± 16.4	80.8	46.6 - 80.8
BSA (m^2)	1.9 ± 0.25	1.9	1.3 - 2.3
Karnofsky performance status	78.6 ± 9.7	80	60 - 100

Pharmacokinetics:

Pharmacokinetic analyses show dose-dependent linear systemic exposure with a short plasma 1-2 h terminal half-life; Cmax at the highest dose tested (cohort 7, 40 mg/m^2) ranged from 1130 to 739 ng/mL (7.7 to 5.1 µM). *In vitro* studies indicate µM concentrations of DAG are effective against various glioma cell lines. In Figure 4 below, PK profile from the literature after 50 mg/m^2 dose (Eagan et al 1982) is also included to compare current trial data with historical data. Figure 5 shows the Dose-AUC relationship.

Fig 4. PK by dose cohort & published literature

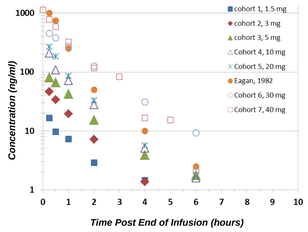
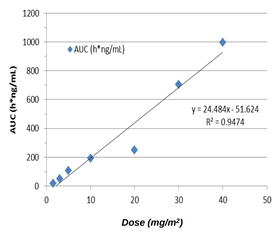


Fig 5. Dose-AUC relationship



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 5.
Estimated Tumor Concentration in Human Brain Exceeds in vitro IC_{50}

Dose and Dosing Day of Each Cycle Current Trial	Plasma Cmax *(µg/mL)*[1]	Estimated Maximum Tumor Concentration in Brain [2,3] *(µg/g tissue)*	*µM**	IC_{50} in GBM Cell Lines *µM*
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

1. From study DLM-10-001, cohort #7; PK was conducted only on Day 1, given the short t-1/2 of ~1h Cmax is assumed to be same for Day 2 & 3.
2. Percent of plasma drug concentration in brain tumor = 44%, Eckhardt, 1977
3. Half-life of drug in human brain tumor tissue = 20h, Eckhardt, 1977

*Volume of 1 g tissue assumed to be 1 mL

Anti-tumor Activity

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 patients exhibiting stable disease or tumor regression allowed to remain on study drug. 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. These interim results support the continued development of VAL-083 as a potential treatment to extend patient survival and improve quality of life.

Historical NCI-sponsored studies achieved promising results in newly diagnosed and recurrent GBM using a dosing regimen of 25 mg/m2/day for five days every five weeks. Historically, toxic effects were noted on white blood cell (WBC) and platelet counts. For example, Egan etal (1979) observed nadir of 2,100/µL (lymphopenia) and 88,000/µL (thrombocytopenia), respectively. In a separate study, a dose of 40mg/m^2/day for five days resulted in a median platelet nadir of 31,000/µL and WBC nadir of 2,300/µL. 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 patient outcomes. We have now achieved significantly higher doses in comparison to the NCI regimen without encountering dose limiting toxicity.

Table 3.
Comparison of recent & planned dose cohorts (6 – 9) of VAL-083 to historical NCI GBM regimen

DOSE & STUDY	Single Dose	Acute Regimen *(single cycle)*		Comparative Dose (@ 35 days)	Dose Density (dose per week)	Status
NCI GBM (Eagan) 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	30mg/m^2/wk	No DLT
	40 mg/m^2		120 mg/m^2	240 mg/m^2	40mg/m^2/wk	No DLT
	50 mg/m^2		150 mg/m^2	300 mg/m^2	50mg/m^2/wk	ongoing
	60 mg/m^2		180 mg/m^2	360 mg/m^2	60mg/m^2/wk	planned

Safety & Tolerability:

We have observed NCI-CTCAE Grade 1 lymphopenia (LLN to >3,000/µL) and thrombocytopenia (platelet counts LLN to >75,000/µL) at doses above 20mg/m^2/day x 3 days.

Table 4.
Hematologic adverse events observed in GBM patients to date

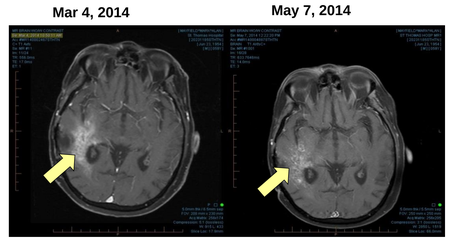
Cohort	dose & hemalogic toxicity	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
1 - 4	**up to 10 mg/m^2**						
	LYMPHOPENIA	*0*	*0*	*0*	*0*	*0*	*0*
	THROMBOCYTOPENIA	*0*	*0*	*0*	*0*	*0*	*0*
5	**20 mg/m^2**						
	LYMPHOPENIA	*1 (25%)*	*0*	*0*	*0*	*0*	*1 (25%)*
	THROMBOCYTOPENIA	*0*	*0*	*0*	*0*	*0*	*0*
6	**30 mg/m^2**						
	LYMPHOPENIA	*0*	*0*	*0*	*0*	*0*	*0*
	THROMBOCYTOPENIA	*1 (33%)*	*0*	*0*	*0*	*0*	*1 (25%)*
7	**40 mg/m^2**						
	LYMPHOPENIA	*1 (33%)*	*0*	*0*	*0*	*0*	*1 (25%)*
	THROMBOCYTOPENIA	*0*	*0*	*0*	*0*	*0*	*0*
8	**50 mg/m^2**	**Ongoing**					
9	**60 mg/m^2**	**TBD if no DLT @ 50mg/m^2**					

Based on these data, we have continued dose escalation to 50mg/m^2/day x 3 days. MTD will be established by dose limiting toxicity (DLT), defined as:

a) Hematologic DLT
   i. Grade 4 thrombocytopenia (platelets <25,000/µL), or Grade 3 thrombocytopenia (platelets <50,000 -25,000/µL with hemorrhage);
   ii. Absolute neutrophil count (ANC) nadir < 500/µL or platelet count <50,000/µL, either lasting for more than five days;
   iii. ANC < 500/µL with fever (febrile neutropenia); or
   iv. Treatment delays of greater than 3 weeks for hematologic toxicity

b) Non-hematologic DLT
   i. Any grade 3 or 4 non-hematologic toxicity due to treatment with the exception of alopecia, nausea, and vomiting;
   ii. Grade 3 or 4 nausea or vomiting while receiving an optimal antiemetic regimen for prophylaxis and management;
   iii. Treatment delays of greater than 3 weeks for toxicity

Fig 6: 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.



CONCLUSIONS & NEXT STEPS:

- **VAL-083 is a cytotoxic alkylating agent with a unique bi-functional mechanism that overcomes temozolomide 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**
- **VAL-083 is well tolerated at doses up to 40mg/m^2; no drug-related SAEs have been observed in the current Phase I/II clinical trial**
- **Exploration at higher doses is warranted. Enrollment and analysis of the 50mg/m^2 dose cohort is ongoing.**
- **Based on historical data and recent observations, VAL-083 demonstrates promise as potential therapy for GBM patients who fail or are unlikely to respond to current standard-of-care.**