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

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Abstract #TPS2109: 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. Previous clinical studies suggest that VAL-083 has anti-tumor activity against a range of cancers including GBM. In *in vitro* studies, VAL-083 demonstrated activity in pediatric and adult GBM cell lines, as well as GBM cancer stem cells. Notably, VAL-083 overcomes resistance to MGMT *in vitro*. In light of extensive safety data from clinical trials and promising efficacy in CNS tumors, DelMar 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. Dose limiting toxicity is expected to be myelosuppression, the management of which has improved in recent years. 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 (Eagan, et al. 1979). In the present study, the cumulative dose in a 33 day cycle ranges from 9 mg/m^2 (cohort 1) to 240 mg/m^2 (cohort 7). Five dose cohorts, with the highest 33 day cycle cumulative dose of 120 mg/m^2, have completed the trial with no drug-related serious adverse events: MTD was not yet reached. Enrollment for cohort 6 (33 day cumulative dose: 180 mg/m^2) has been initiated. The final cohort of this study, cohort 7 (33 day cumulative dose: 240 mg/m^2), will be initiated subject to no DLT in cohort 6; the results will determine the design of the safety and efficacy registration trial. **Methods:** 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 been treated with surgery and/or radiation, if appropriate, must have failed both bevacizumab and temozolomide, unless contraindicated. **ClinicalTrials.gov Identifier:** NCT01478178

Conclusions

- **VAL-083 demonstrated promising clinical activity against newly diagnosed and recurrent GBM in historical NCI-sponsored clinical trials**
- **VAL-083 has potent MGMT-independent cytotoxic activity against GBM cell lines *in vitro***
- **Pharmacokinetic analyses show dose-dependent increase in exposure with a short plasma 1-2 h half-life and a Cmax of <265ng/mL (1.8µM) at 20mg/m^2 (see figure 2)**
- **PK data is consistent with literature from previous trials, suggesting activity of VAL-083 in brain tumors; plasma concentration achieved in the 20 mg/m^2 cohort is sufficient to inhibit glioma cell growth *in vitro***
- **VAL-083 therapy is well tolerated to date; no drug-related serious AEs have been detected**
- **MTD has not been reached after completion of cohort 6 (30 mg/m^2); enrollment and analysis of cohort 7 (40 mg/m^2) is ongoing**
- **DelMar will be filing an amendment with FDA to allow dosing beyond 40 mg/m^2 subject to not reaching MTD in cohort 7**

Results and Observations to Date (study ongoing): No drug-related serious adverse events have been detected, and maximum tolerated dose (MTD) has not been reached at doses up to 30 mg/m^2. Enrollment and evaluation of Cohort 7 (40mg/m^2) is ongoing. Higher doses may be enrolled subject to completion of mandated safety observation period with Cohort 6 (30mg/m^2). Patients enrolled present with refractory progressive GBM and a dire prognosis. All GBM patients enrolled to date have failed front-line temozolomide and all except one had failed second-line bevacizumab therapy. The primary endpoint of this portion of the study is to determine a modernized dosing regimen for advancement to registration-directed clinical trials. Tumor volume is measured after every second cycle and patients exhibiting any evidence of continued progression at any time during the study are discontinued, but cycle 1 toxicity is captured for MTD determination. In this design, it is not possible to perform a rigorous assessment of patient benefit due to slowed tumor growth. Tumor volume is assessed during the study based on RANO criteria. Two patients exhibiting a response (stable disease or partial response) reported in early cohorts improved clinical signs with a maximum response of 28 cycles (84 weeks) prior to discontinuing due to adverse events unrelated to study. To date, one of two patients in cohort 6 (30 mg/m^2) exhibited stable disease after 1 cycle of treatment. Outcomes analysis of cohort 6 is ongoing. These preliminary data support continued exploration of higher dose cohorts.

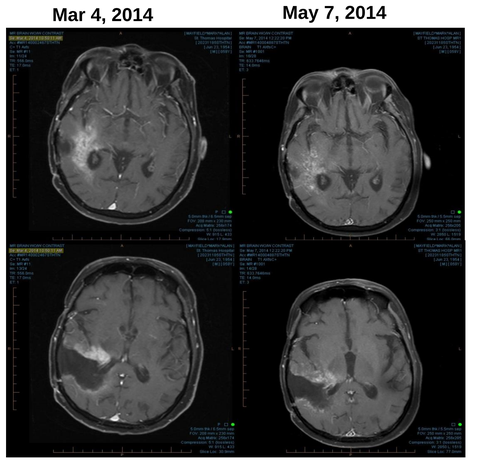

Figure 3: MRI scans of patient # 26 before (March 4, on the left), and after (May 7, on the right) 2 cycles of VAL-083 treatment. Thick confluent regions of abnormal enhancement have diminished, now appearing more heterogeneous.

***Table 4.* Summarizes the dosing schedule for the trial**

Dose Escalation Scheme (mg/m^2)		Patients Treated	Status	Cumulative dose in 33-day cycle (comparison to NCI historical regimen of 125 mg/m^2 per cycle)
Original	**Revised**			
1.5	**1.5**	3	Completed – No DLT	9 mg/m^2
3.0	**3.0**	4	Completed – No DLT	18 mg/m^2
5.0	**5.0**	10*	Completed – No DLT	30 mg/m^2
10.0	**10.0**	3	Completed – NO DLT	60 mg/m^2
15.0	**20.0**	4	Completed – NO DLT	120 mg/m^2
20.0				
25.0	**30.0**	3	Completed – No DLT Analysis ongoing	180 mg/m^2
30.0				
n/a	**40.0**	3 (planned)	Enrolling	240 mg/m^2

***Cohorts 2 and 3 were expanded to allow for patient demand and to gather additional data on CNS metastases patients.**

Current situation: GBM is the most deadly form of human brain cancer, with a median survival for patients with recurrent GBM of 6 months. High expression of MGMT (O6-methylguanine-DNA methyltransferase) is strongly correlated with chemo-resistance to both first-line therapy TMZ and BCNU, and vastly reduces survival.

VAL-083 is a bifunctional alkylating agent causing interstrand DNA crosslinks at the N^7-guanine[3], which is distinct from the mechanisms of other alkylating agents used in GBMHistorical clinical data further suggest comparable or enhanced survival and improved safety compared to TMZ and BCNU and reported absence of cross-resistance between VAL-083 and both TMZ and BCNU, supports the potential efficacy of VAL-083 in the treatment of GBM patients failing other agents.

***Table 2.* Historical clinical data with VAL-083 support the potential for comparable or enhanced survival similar to standard chemotherapy with an improved safety profile in the treatment of GBM.**

GBM Chemotherapy	VAL-083 *Eagan (1979)*	Temozolomide *Stupp (2005)*	Carmustine (BCNU)
Median O.S. (*XRT+chemo*)	67 weeks	58 weeks	40-50 weeks
DLT	Hematologic	Hematologic	Hematologic
Nadir	18-21 days	21-28 days	21-35 days
Recovery	Within 7-8 days	Within 14 days	42-56 days
Other severe toxicities reported (>2%)	none	nausea, vomiting, fatigue, asthenia, neuropathy	pulmonary, nausea, vomiting, encephalopathy, renal

VAL-083 was better than TMZ for inhibiting tumor growth in GBM cell lines SF188, U251, and T98G, activity independent of MGMT (Figure 2). VAL-083 furthermore inhibited the growth of Cancer Stem Cells (BT74, GBM4 and GBM8) by 80-100% in neurosphere growth assays, with minimal effect on normal human neural stem cells (Dr. Dunn, S.E.[4]).

***Table 1.* TMZ resistance and MGMT status in GBM cell lines SF188 (pediatric), U251 (adult), and T98G (adult) (Dr. Dunn, S. E.[4])**

GBM cell line	SF188	U251	T98G
TMZ resistance	++	+	+++
MGMT status	-	-	+

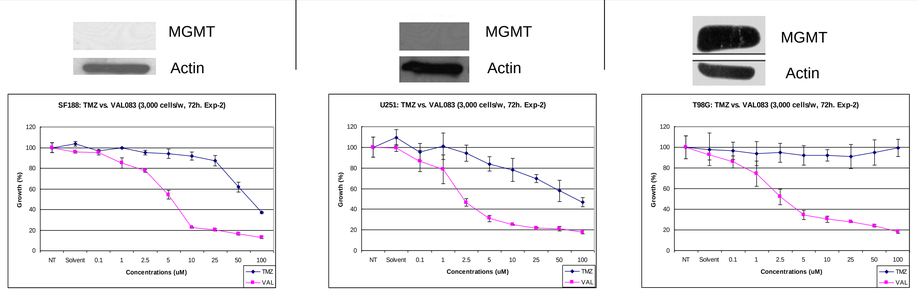

Figure 1. VAL-083 activity against GBM cell-lines SF188, U251 and T98G GBM cells (Dr. Dunn, S.E.[4]).

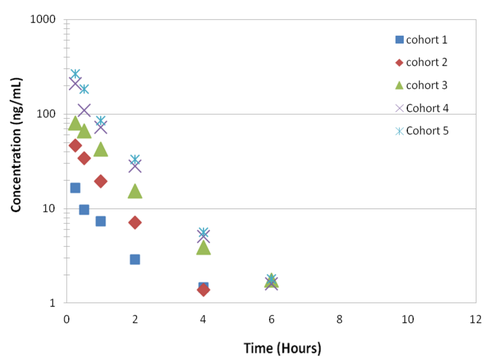

Figure 2. Plasma concentration-time profiles of VAL-083 showing dose-dependent systemic exposure (mean of 3 subjects per cohort).

Pharmacokinetics: Pharmacokinetic analyses show dose-dependent systemic exposure with a short plasma 1-2 h half-life; average Cmax at 20 mg/m^2 is 266 ng/mL (0.18 µg/mL or ~1.8 µM). Pharmacokinetic analyses of cohort 6 (30 mg/m^2) are ongoing. In previous clinical trials using less sensitive bioanalytical methods than today's LC-MS-MS method[5], *iv* infusion of approximately 3-4 times higher doses (60-72 mg/m^2) led to Cmax ranging from 1.9 to 5.6 µg/mL, and the concentration-time curve was bi-exponential, similar to the finding in the current trial. Pharmacokinetics are linear and consistent with previous published data suggesting higher levels can be achieved at higher doses in the current trial. *In vitro* studies indicate that µM concentrations of VAL-083, as obtained in cohorts 4, 5 and 6, are effective against various glioma cell lines (as shown in Figure 1).

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