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

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ABSTRACT # 2023 (ClinicalTrials.gov Identifier: NCT01478178):

Glioblastoma multiforme (GBM) is the most common brain cancer. Front-line systemic therapy with temozolomide is often ineffective due to O^6-methylguanine-DNA-methyltransferase (MGMT)-mediated resistance. Dianhydrogalactitol (VAL-083) is a bi-functional DNA alkylating agent that crosses the blood-brain barrier and overcomes resistance to MGMT *in vitro*. The goal of this Phase I/II clinical trial is to determine an appropriate dose for registration-directed Phase II/III trials in refractory GBM. **Methods:** Open-label, single-arm Phase I/II dose-escalation study in patients with histologically-confirmed GBM, previously treated with radiation and must have failed both bevacizumab and temozolomide (TMZ), unless contraindicated. The study utilizes a 3+3 dose-escalation design. Patients received 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. **Results:** 30 patients have been enrolled across 8 dose cohorts ranging from 1.5 to 50mg/m^2/d. Dose limiting toxicities consisting of grade 4 thrombocytopenia and grade 3 thrombocytopenia with hemorrhage were observed at dose level 8 (50mg/m^2/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) was determined as 40mg/m^2/d. 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 (5.1-7.7µM) at 40mg/m^2/d. Compared to historical trials, the present regimen delivers substantively more drug by C_{max} and dose intensity. A dose intensity of 25 mg/m^2/wk in combination with radiation was previously shown superior to radiation alone against GBM. **Conclusion:** VAL-083 dosing appears limited by myelosuppression. An expansion cohort of up to 14 patients has been initiated at the previous well tolerated dose of 40mg/m^2/d. A small expansion cohort (n=3) at an interim 45mg/m^2/d dose will be studied in parallel with the expansion cohort, and the expansion cohort may be continued at this higher dose if safety data warrants.

PATIENT DEMOGRAPHICS

GBM Patients n = 30	Male = 19
	Female = 11
Age (mean):	*52 +/- 12.6*
KPS (mean):	82 (range 60-100)

Prior Treatments (26 CRFs)	Patients (%)	2x	3x
TMZ	26 (100%)	6	1
BEV	24 (92%)	7	1
Other salvage therapy	20 (77%)		
Multiple salvage therapies	7 (27%)		

MGMT expression was characterized in patients with available tissue (n=5)

Table 3: MGMT expression in DLM-10-001 patients

Unknown	25
Known	5

MGMT expression in patients with known MGMT status		
Unmethylated: *high MGMT expression*	n=5	*100%*
Methylated: *low MGMT expression*	n=0	*0%*

RESULTS AND OBSERVATIONS

The majority of GBM patients survive less than 2 years following diagnosis; median survival is 14.6 months despite best available treatment. Standard treatment includes surgical resection to remove as much of the tumor as possible (debulking) followed by radiotherapy with concomitant and adjuvant chemotherapy with temozolomide. Bevacizumab is approved as a single agent for patients with recurrent GBM following prior therapy as an alternative to corticosteroids to relieve disease symptoms in the US, Canada, Australia and Japan. There are no data demonstrating an improvement in disease-related symptoms or increased survival in refractory GBM with bevacizumab.[5]

Treatment options available for GBM patients whose tumors recur following treatment with bevacizumab are limited. Rapid tumor re-growth or "rebound" and accelerated clinical decline following withdrawal of bevacizumab is observed in many patients and prognosis is extremely poor.

A limited number of retrospective analyses examining survival in the post-bevacizumab failure population have been published. Sakruti et al. (2014) suggested that the median OS from the start of bevacizumab was 12.2 months (95% CI, 10.0, 14.3) with no significant difference in OS whether bevacizumab therapy was initiated following first, second or later GBM recurrence.[6] Iwamoto et al. (2009) examined overall survival of GBM patients following bevacizumab failure and noted that median OS for patients receiving a range of salvage chemotherapy was 5.2 months (95% CI, 3.3, 8.4) while patients receiving supportive care only had a median survival of 2 months (95% CI 1.3, 3.3).[7]

All GBM patients enrolled in DelMar's Phase I/II clinical trial failed prior treatment with standard front-line (TMZ + XRT) and 92% also failed bevacizumab (BEV). 77% also failed one or more courses of additional salvage therapy beyond TMZ and BEV prior to enrollment. Patients were not re-resected prior to treatment with VAL-083 and therefore have a growing glioblastoma at the time of treatment. MGMT expression was characterized for patients whose data or tissue blocks were available for analysis. All patients whose tumors were characterized (n=5) had an unmethylated MGMT promotor, which is correlated with poor patient outcomes (Table 3).[2]

VAL-083 was well tolerated at lower doses using a regimen of daily x 3 every 21 days. Adverse events typically mild to moderate; no treatment-related serious adverse events at dose up to 40 mg/m^2 daily x 3 every 21 days. DLT was observed in two of six (33%) of patients at 50 mg/m^2 daily x 3 every 21 days, indicating that 50 mg/m^2 daily x 3 every 21 days is above the MTD. Dose limiting toxicity was defined by thrombocytopenia (low platelet counts), with nadir occurring at approximately day 21. Generally, DLT-related symptoms resolved rapidly and spontaneously without concomitant treatment, although one patient who presented with hemorrhoids received a platelet transfusion as a precautionary measure. Additional myelosuppression was observed in the 50mg/m^2 cohort; however, none of these was considered a DLT (Table 1).

In the dose-escalation portion of DelMar's clinical trial, patients were withdrawn from the study at any sign of radiographic progression. To continue treatment, stable disease or tumor regression must be observed at the first post-treatment MRI, which was conducted after one or two cycles of treatment. The median number of treatment cycles with VAL-083 received in the dose-escalation portion of the trial was two, with seven patients (24%) receiving only one cycle of treatment and six patients (21%) receiving more than two cycles of VAL-083.

As expected, the near-immediate radiographic observation of tumor stabilization or regression was rare, with only six GBM patients receiving more than two cycles of treatment (median PFS = 1.2 – 1.4 mos.); however, consideration should also be given to the potential of slowed tumor growth following limited treatment and the potential impact on patient survival. Notably, median survival increased in a dose-dependent manner (median OS = 4.4 mos. at <10 mg/m^2 and 9.0 mos. at ≥30mg/m^2). These data suggest that a regimen of VAL-083 ≥30mg/m^2 daily x 3 every 21 days may provide a survival benefit in GBM patients with refractory GBM, including in comparison to published outcomes (fig 3 & 4).

The primary goal of this Phase I/II clinical trial is to confirm a dosing regimen for advancement into registration-directed Phase II/III clinical trials. Based on the limitations of this trial design, these observations suggesting clinical activity or improved outcomes must be considered anecdotal, yet promising.

SAFETY AND TOXICITY

Table 1. **Hematologic toxicities observed in patients in DLM-10-001 trial (CTCAE Grading).**

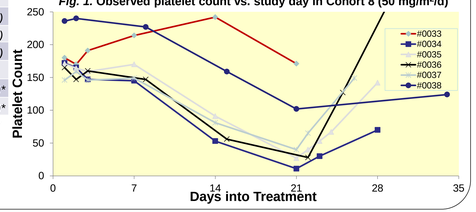
Cohort		Cohort 1-5	Cohort 6	Cohort 7	Cohort 8
Dose		≤ 20mg/m^2	30mg/m^2	40mg/m^2	50mg/m^2
Anemia *(Hct; Hg)*	G1	-	-	1/3 *(33.3%)*	5/6 *(83.3%)*
	G2	-	-	-	-
	G3	-	-	-	-
	G4	-	-	-	-
Leukopenia *(WBC)*	G1	-	1/3 *(33.3%)*	1/3 *(33.3%)*	3/6 *(50.0%)*
	G2	-	-	-	2/6 *(33.3%)*
	G3	-	-	-	2/6 *(33.3%)*
	G4	-	-	-	-
Neutropenia *(neutrophils)*	G1	-	-	1/3 *(33.3%)*	2/6 *(33.3%)*
	G2	-	-	-	-
	G3	-	-	-	1/6 *(16.6%)*
	G4	-	-	-	1/6 *(16.6%)*
Thrombocyto-penia *(platelets)*	G1	-	2/3 *(66.6%)*	2/3 *(66.6%)*	1/6 *(16.6%)*
	G2	-	-	-	-
	G3	-	-	-	3/6 *(50.0%)**
	G4	-	-	-	1/6 *(16.6%)**

**DLT observed in 2 of 6 (33.3%) patients in cohort 8, as defined by Grade 4 thrombocytopenia in 1 of 6 patients (16.6%) and Grade 3 thrombocytopenia with hemorrhage in 1 of 6 patients (16.6%).*

Table 2. **VAL-083 optimized dosing regimen used in DLM-10-001. Comparison to historical NCI regimen (Eagan 1979)[1]**

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

Fig. 1. **Observed platelet count vs. study day in Cohort 8 (50 mg/m^2/d)**



PHARMACOKINETICS:

Fig 2. **PK by dose cohort & published literature[3]**

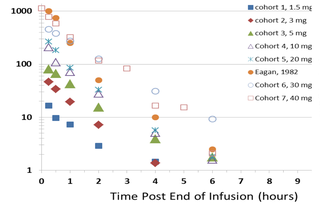


Fig 3. **Dose-AUC relationship**

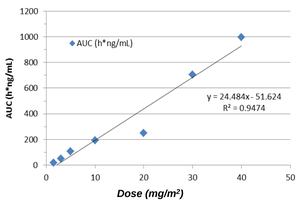


Table 4. **Estimated Tumor Concentration in Human Brain Exceeds *in vitro* IC_{50}**

Dose and Dosing Day of Each Cycle Current Trial	Plasma Cmax *(µg/mL)*[a]	Estimated Maximum Tumor Concentration in Brain [b,c]		IC_{50} in GBM Cell Lines**
		(µg/g tissue)	*µM**	*µM*
40mg/m^2 Day-1	0.781	0.344	2.36	1.8-4.5
40mg/m^2 Day-2	0.781	0.503	3.45	1.8-4.5
40mg/m^2 Day-3	0.781	0.563	3.86	1.8-4.5

a. 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.
b. Percent of plasma drug concentration in brain tumor = 44%, Eckhardt, 1977[4]
c. Half-life of drug in human brain tumor tissue = 20h, Eckhardt, 1977[4]
*Volume of 1 g tissue assumed to be 1 mL
**IC_{50} range for low MGMT (U251 and SF188) and high MGMT (T98G) GBM cells tested

Fig 3. **Survival of Patients GBM Treated with VAL-083 from Initiation of BEV Compared to Predicted Survival (DLM-10-001 all dose cohorts)**

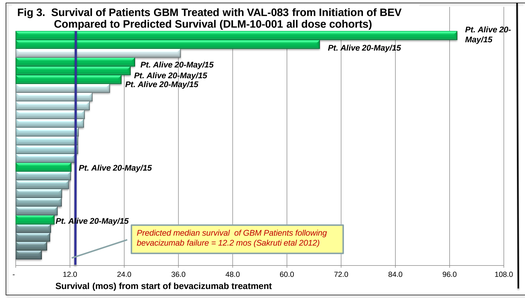
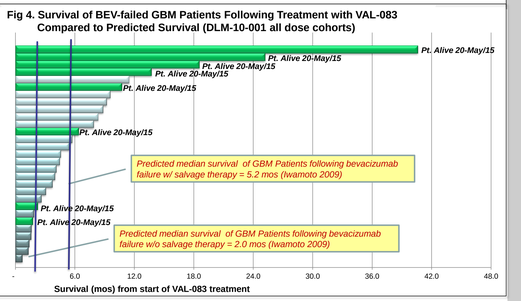


Fig 4. **Survival of BEV-failed GBM Patients Following Treatment with VAL-083 Compared to Predicted Survival (DLM-10-001 all dose cohorts)**



At time of analysis:

- Median PFS in refractory GBM with VAL-083 is short (1.2 – 1.4 months); however, preliminary analysis shows increasing dose-dependent median survival with increasing dose of VAL-083 with median survival ~9.0 months at doses ≥30mg/m^2 daily x 3 every 21 days vs. 4.4 months at doses <10mg/m^2 daily x 3 every 21 days
- 6 month OS following initiation of VAL-083 treatment across all dose cohorts: 41.4%, with two additional patients from later cohorts still alive, but have not yet reached 6 month OS
- 12 month OS following initiation of VAL-083 treatment across all dose cohorts: 17.2%, with four additional patients from later cohorts still alive, but have not yet reached 12 month OS
- 10% of patients treated with VAL-083 had longer time to progression than prior treatment with bevacizumab
- 59% of patients treated with VAL-083 survived longer than predicted following initiation of bevacizumab therapy[6]
- 75% of patients treated with VAL-083 survived longer than predicted following failure of bevacizumab therapy with supportive care[7] and 48% of patients treated with VAL-083 survived longer than predicted following failure of bevacizumab and subsequent treatment with a range of salvage therapies[7]

CONCLUSIONS & NEXT STEPS:

- **Based on analysis of hematologic toxicity data, it is likely that a dose of 50 mg/m^2/d x 3days in a 21 day cycle is above the MTD.**
- **PK data suggests that a dose of 40 mg/m^2/d achieves concentrations of VAL-083 in the CNS at or above the IC50 observed for multiple GBM cell lines *in vitro*.**
- **Preliminary analysis shows increasing dose-dependent median survival with median OS = ~9.0 months at doses ≥30 mg/m^2/d x 3days in a 21 day cycle**
- **In accordance with the protocol, an expansion cohort of up to 14 patients has been initiated at the well-tolerated dose of 40 mg/m^2/d. An additional cohort (n=3) at an interim 45mg/m^2/d dose will be studied in parallel with the expansion cohort, and the expansion cohort may be continued at this higher dose if safety data warrants.**
- **Activities related to design of a proposed registration-directed Phase II/III trial have been initiated. The goal of the registration trial will be to examine the impact of extended VAL-083 treatment on OS and radiographic tumor response in patients with refractory GBM.**

References:

1. Eagan R.T. et at. JAMA 1979; 241 (19), 2046-50
2. Hegi et al. N Eng J Med; 2005; 352 (10): 987-96
3. Eagan R.T. et al. Cancer Treat Rep. 1982; 66(8):1647-49.
4. Eckhardt et al. Cancer Treat Rep. 1977; 61(5):841-7
5. As stated in Avastin (Bevacizumab) prescribing Information: http://www.gene.com/download/pdf/avastin_prescribing.pdf
6. Sakruti, S. et al. (2014). ASCO Abstract No. 95194.
7. Iwamoto F. et al. Neurology 2009; 73(15) 1200-1206.