Phase I/II Study of VAL-083 in Patients with Recurrent Malignant Glioblastoma Multiforme

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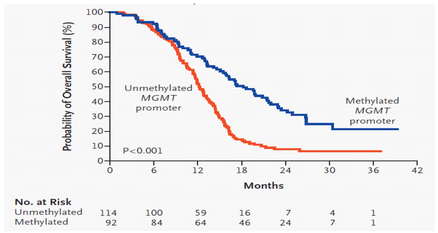
Abstract # CT404: Median survival for patients with recurrent glioblastoma multiforme (GBM) is less than 6 months. Front-line systemic therapy is temozolomide, but chemo-resistance due to O^6-methylguanine-DNA-methyltransferase (MGMT) activity has been implicated in poor outcomes. VAL-083 is a structurally unique bi-functional DNA alkylating small molecule drug that crosses the blood-brain barrier and accumulates in brain tumor tissue. Previous human clinical studies by several investigators have suggested that VAL-083 has anti-tumor activity against a broad range of tumor types including GBM. In preclinical *in vitro* studies, VAL-083 demonstrated activity in a wide range of cancer cell lines, including pediatric and adult GBM cell lines and GBM cancer stem cells. Notably, VAL-083 overcomes chemo-resistance to MGMT *in vitro.* In light of extensive safety data from several clinical trials and promising efficacy signals in CNS tumors, DelMar initiated a new clinical study to determine the safety, tolerability, pharmacokinetics, anti-tumor activity in patients with recurrent GBM.

This is an 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 *i.v.* on days 1, 2, and 3 of a 21 day cycle. GBM patients have previously been treated with surgery and/or radiation, if appropriate, and must have failed both bevacizumab and temozolomide, unless contraindicated. In the ongoing trial, cohorts 1 through 5 (20 mg/m^2) have completed the trial successfully with no drug-related serious adverse events (SAEs), and maximum tolerated dose (MTD) was not yet reached. Enrollment for Cohort 6 (30 mg/m^2) is ongoing. Pharmacokinetic analyses show dose-dependent increase in exposure with a short 1-2 hour plasma half-life and a Cmax of <265 ng/ml at 20 mg/m^2. Historical data suggests a long half-life in the cerebrospinal fluid (CSF) (>20 hours) with preferential accumulation to brain tumor tissue. MGMT status of patients and drug concentration in the CSF are being evaluated when possible.
ClinicalTrials.gov Identifier: NCT01478178

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 (Figure 1).



Source: Hegi ME et al. N Engl J Med. 2005; 352(10):997-1003.

Figure 1: Correlation of MGMT promoter methylation with overall survival for patients with GBM

Conclusions:

- **Treatment of recurrent GBM remains a significant unmet medical need**
- **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 table 3)**
- **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 5 (20 mg/m^2); enrollment and analysis of cohort 6 (30 mg/m^2) is ongoing**

VAL-083 is a bifunctional alkylating agent causing methylation of N^7-guanine and interstrand DNA crosslinks[3], which is believed to be distinct from the mechanisms of other alkylating agents (e.g. TMZ or BCNU). 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 these other agents. Historical clinical data further suggest comparable or enhanced survival and improved safety compared to TMZ and BCNU.

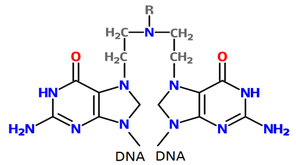


Figure 3. N7 guanine interstrand crosslinked DNA

***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, and the activity of VAL-083 was 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	-	-	+

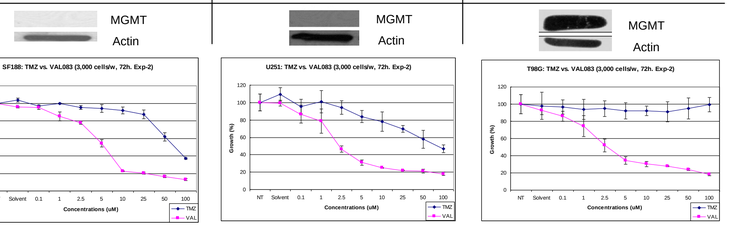


Figure 2. VAL-083 activity against GBM cell-lines SF188, U251 and T98G GBM cells (Dr. Dunn, S.E.[4]).

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 20 mg/m^2. Enrollment and evaluation of Cohort 6 (30mg/m2) 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. No assessment of patient benefit due to slowed tumor growth is possible in this design. To date, all patients treated in cohorts 1-5 have discontinued due to tumor progression or adverse events unrelated to study drug. Tumor volume is assessed during the study based on RANO criteria. Two 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 preliminary data support continued exploration of higher dose cohorts.

***Table 3.* Pharmacokinetics VAL-083 in Brain Tumor Patients**

Cohort	Dose mg/m^2	Tmax h	Cmax ng/mL	Cmax (µM)	AUC ng*h/mL	t-1/2* h
1	1.5	0.25	16.5	0.11	18.9	2.02
2	3	0.25	46.4	0.32	48.5	0.83
3	5	0.25	80.5	0.55	108.0	1.27
4	10	0.25	172.0	1.18	191.7	1.19
5	20	0.25	265.5	1.82	249.9	1.22

*Terminal half-life, lambda z. All values are mean of 2-4 patients.

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). 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. The observed pharmacokinetics in this trial thus follow that which would be predicted by previously published data. *In vitro* studies indicate that µM concentrations of VAL-083, as obtained in cohorts 4 and 5, are effective against various glioma cell lines.

***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 (planned)	Enrolling/ analysis ongoing	180 mg/m^2
30.0				
n/a	**40.0**	3 (planned)	To be initiated subject to no DLT in 30mg/m^2 dose	240 mg/m^2

***Cohorts 2 and 3 were expanded to allow for patient demand and to gather additional data on CNS metastases patients.**
****NCI dosing regimen was 25mg/m^2 x 5 days with a 28-day nadir+recovery window between doses (total=33 day cycle). This dosing regimen is for 3 days every 3 weeks (six doses in a given 33-day period).**

References:

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