Phase I/II Study of Dianhydrogalactitol in Patients with Recurrent Glioblastoma

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ABSTRACT

BACKGROUND: Glioblastoma (GBM) is the most common CNS tumor. Patients with recurrent GBM have few treatment options and dismal prognosis. High expression of O^6-methylguanine-DNA-methyltransferase (MGMT) is correlated with resistance to front-line systemic therapy with temozolomide (TMZ) and poor patient outcomes. Dianhydrogalactitol (VAL-083) is a bi-functional alkylating agent that readily crosses the blood-brain barrier and has demonstrated activity independent of MGMT in multiple GBM cell lines and cancer stem cells *in vitro*. VAL-083 showed promise against CNS tumors in prior NCI-sponsored clinical trials. The goal of this clinical trial is to determine the appropriate dose for VAL-083 for advancement to Phase III trials as a new treatment for recurrent GBM.

METHOD: Study Population: Patients must have recurrent GBM following surgery, radiation, TMZ and bevacizumab. Phase I: Open-label, single-arm dose-escalation study (3+3 design). Patients received VAL-083 IV on days 1, 2, 3 of a 21-day cycle, until MTD was reached. Phase II: 14 additional patients enrolled at MTD to further assess safety and outcomes.

RESULTS: Phase I: 34 patients were enrolled in escalating dose cohorts (1.5 - 50 mg/m^2/d) and 40 mg/m^2/d confirmed as the MTD. Myelosuppression was mild; no drug-related serious adverse events were reported at doses ≤40 mg/m^2/d. Dose limiting toxicity (G4 thrombocytopenia) was observed at higher doses. Platelet nadir occurred around day 20 and resolved rapidly and spontaneously. A dose-related and clinically meaningful survival improvement was observed. Pharmacokinetic analyses show dose-dependent linear systemic exposure with short 1-2h plasma terminal half-life; average C_{max} 781 ng/mL at 40 mg/m^2/d. Phase II: 14 patients have been enrolled at 40 mg/m^2/d. To date, safety observations in the Phase II cohort are consistent with Phase I.

CONCLUSIONS: VAL-083 at 40 mg/m^2/d exhibits a favorable safety profile and a dose-related trend toward clinically meaningful improved survival in refractory GBM patients was observed in Phase I. We expect to present median overall survival in the Phase II expansion cohort and proposed Phase III study design. **ClinicalTrials.gov Identifier** NCT01478178.

VAL-083 Mechanism of Action

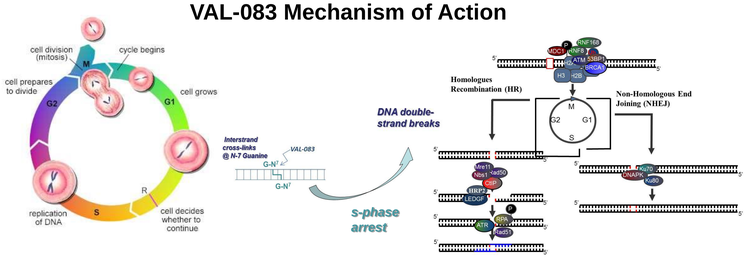
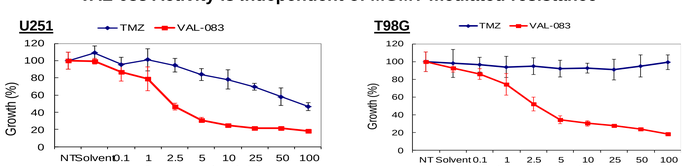


Figure 1: VAL-083 crosslinks DNA at N7-position of guanine leading to S/G2 cell cycle arrest, double strand DNA breaks and apoptosis in cancer cells. *Zhai et al. AACR annual meeting 2016*

VAL-083 Activity is Independent of MGMT-mediated resistance



GBM Cell Line	***U251***	***T98G***
MGMT promoter methylation	Methylated (low expression)	Unmethylated (high expression)
IC_{50} VAL-083	2.5μM	2.5μM
IC_{50} TMZ	10.0μM	>>100μM

Figure 2: TMZ vs. VAL-083 in Adult GBM Cell Lines (3000 cells/well, 72-h exposure). *Hu et al. AACR annual meeting 2012*

VAL-083 Activity Against GBM Cancer Stem Cells

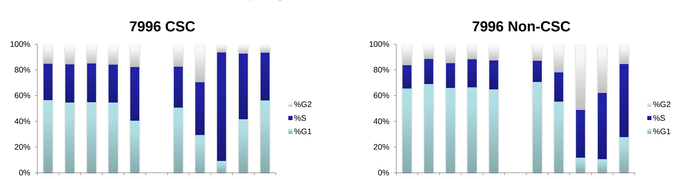
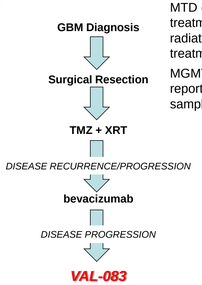


Figure 3: VAL-083 is active against TMZ resistant stem and non-stem cell GBM cultures at single μM doses *Fouse et al. SNO annual meeting 2014*

Summary Results: Phase I/II in Refractory Glioblastoma Multiforme: *clinicaltrial.gov identifier: NCT01478178*

Overview



Forty eight (48) GBM patients enrolled, including 34 in a Phase 1 dose escalation and a 14 patient Phase 2 dose expansion at MTD (40mg/m^2). Forty-eight of 48 (100.0%) GBM subjects enrolled in the Phase 1 and 2 portions of the study had prior treatment with temozolomide, 47 (97.9%) had received prior radiation therapy, 42 (87.5%) had received both temozolomide and radiation therapy, 46 (95.8%) had previously received treatment with bevacizumab, and in 10 (20.8%) GBM subjects, prior treatment consisted of only temozolomide and bevacizumab.

MGMT methylation status was characterized by PCR and/or ELISA for nineteen GBM patients enrolled the trial; IDH1 status was reported in eleven patients. Of patients tested, 84% exhibited high MGMT and 90% were wild-type IDH1. All patients whose samples were tested for both markers were MGMT unmethylated by PCR and wild-type IDH1.

Table 1 *Prior Treatment of 48 GBM Patients in DLM-10-001*

Temozolomide (TMZ)	48 *(100%)*	Bevacizumab (BEV)	46 *(95.8%)*
Radiotherapy (XRT)	47 *(97.9%)*	Failed TMZ + BEV	46 *(95.8%)*
TMZ + XRT	47 *(97.9%)*	OTHER TREATMENTS	38 *(79.2%)*

Table 2. *MGMT and IDH1 mutation status in DLM-10-001*

MGMT Status (n = 19)		IDH1 Status (n = 11)		Both Reported (n = 4)
Unmethylated / High MGMT (>67 ng MGMT/mg total protein)	84.2%	Wild Type:	90.9%	Unmethylated & IDH1^{wt}: 100%
Methylated / Low MGMT (<45ng MGMT/mg total protein)	15.8%	Mutant:	9.1%	

Safety & Pharmacokinetics

Patients received intravenous VAL-083 administered on the first three days of every three week cycle. With one exception, no serious adverse events (SAEs) related to study drug were encountered among GBM patients at VAL-083 doses up to 40 mg/m^2/day whereas related SAEs were observed at VAL-083 doses of 45 and 50 mg/m^2/day . One subject previously treated with CCNU reported Grade 4 thrombocytopenia (platelet count 10,000/μL on Day 17) at 40mg/m^2/day. As a result, the protocol inclusion criterion for platelet count was increased to 150,000/μL for patients receiving prior nitrosourea within 12 weeks prior to enrollment.

Pharmacokinetic (PK) analyses show dose-dependent linear systemic exposure with a short plasma 1-2h terminal half-life; average C_{max} at 40 mg/m^2/d was 781 ng/mL (5.3 μM). The observed PK profile is comparable to published literature. Eagan et al. Cancer Treat Rep. 1982

TABLE 3: *VAL-083 Safety Observations Phase I/II Clinical Trial*

Hematologic parameter and CTCAE grade	dose	≤30 mg/m^2		40 mg/m^2		45 mg/m^2		50 mg/m^2	
	n	20		17		4		7	
Anemia	≤G2	11	55%	2	12%	2	50%	6	86%
	G3	2	10%	0	0%	0	0%	0	0%
	G4	0	0%	0	0%	0	0%	0	0%
Leukopenia	≤G2	5	25%	2	12%	0	0%	5	71%
	G3	1	5%	0	0%	0	0%	3	43%
	G4	0	0%	0	0%	2	50%	0	0%
Neutropenia	≤G2	4	20%	0	0%	0	0%	0	0%
	G3	0	0%	0	0%	0	0%	3	43%
	G4	0	0%	0	0%	2	50%	1	14%
Thrombocytopenia	≤G2	9	45%	3	18%	0	0%	3	43%
	G3	0	0%	0	0%	1	25%	3	43%
	G4	0	0%	1	6%	2	50%	1	14%
DLT Observed		nil		1		2		2	

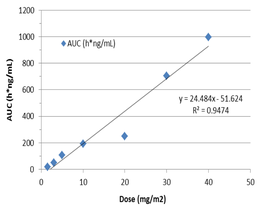


Figure 4: Observed Dose-AUC relationship

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

Dose (day 1,2,3 in 21 day cycle)	Plasma Cmax (μg/mL)[1]	Estimated Maximum Tumor Concentration in Brain (day 3)[2] (μg/g tissue)	IC_{50} in GBM Cell Lines μM	
			μM	
40 mg/m^2/d	0.781	0.563	3.86	2 – 4

1. 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% and half-life of drug in human brain tumor tissue = 20h. Eckhardt et al. Cancer Treat Rep. 1977

*Volume of 1 g tissue assumed to be 1 mL

Survival Analysis

Five of 48 (10.5%) of GBM patients enrolled in the study were reported to have stable disease as their best response following treatment of VAL-083; 43 (89.5%) GBM subjects reported progressive disease. Ad-hoc sub-group analysis of the Phase 1 (dose-escalation) part of the study supports an observed dose response trend. Increased survival was observed at 6, 9 and 12 months following treatment initiation in the high-dose sub-group (30 & 40 mg/m^2) compared to the low dose sub-group (Up to 5 mg/m^2).

TABLE 5: *Comparison of Low vs. High Dose Groups Phase 1*

Dose Cohort Subgroups	6 months	9 months	12 months
High (30 & 40 mg/m^2 n=6)	67%	67%	33%
Low (up to 5 mg/m^2 n=10)	44%	33%	22%

Preliminary analysis of all patients receiving an assumed therapeutic dose of VAL-083 (≥20mg/m^2) suggests that VAL-083 may offer improved survival for GBM patients following bevacizumab failure in comparison to results from published studies.

TABLE 6: *VAL-083 compared to published literature*

Reference	Post Avastin Salvage Therapy	Median Survival from Bevacizumab Failure
Rahman *(2014)*	nitrosourea	4.3 months
Mikkelson *(2011)*	TMZ + irinotecan	4.5 months
Lu *(2011)*	dasatinib	2.6 months
Reardon *(2011)*	etoposide	4.7 months
Reardon *(2011)*	TMZ	2.9 months
Iwomoto *(2009)*	various	5.1 months
DLM-10-001	***VAL-083 (n=22)***	**8.35 months**

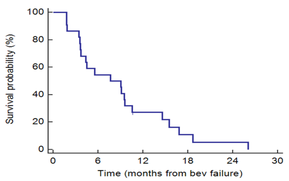


Figure 5: Kaplan Meier plot of patients receiving ≥20mg/m^2 VAL-083

Conclusions and Next Steps

A dose of 40 mg/m^2/day VAL-083 administered on the first three days of every three week cycle is well tolerated in refractory GBM patients and has been selected for study in subsequent clinical trials. Results to date support the potential of a VAL-083 to offer a clinically meaningful survival benefit and a promising new treatment option for GBM patients who have failed or are unlikely to respond to currently available chemotherapeutic regimens.

Three additional clinical trials are planned:

1. A pivotal, randomized Phase 3 study measuring survival outcomes compared to a "physicians' choice" control, which, if successful, would serve as the basis for a New Drug Application (NDA) submission for VAL-083. The control arm will consist of a limited number of salvage chemotherapies currently utilized in the treatment of bevacizumab-failed GBM.
2. A randomized, non-comparative, biomarker-driven, Phase 2 study to determine if treatment of MGMT-unmethylated recurrent GBM with VAL-083 or CCNU improves overall survival at 9 months, compared to historical control in bevacizumab naïve patients. (clinicaltrials.gov identifier: NCT02717962)
3. A single arm Phase 2 clinical trial to confirm the tolerability of DelMar's dosing regimen in combination with radiotherapy (XRT) and to explore the activity of VAL-083 in newly diagnosed MGMT-unmethylated GBM patients whose tumors are known to express high levels of MGMT.

Future Vision: A New Paradigm for GBM