Clinical Trials of VAL-083 in Patients with Chemo-Resistant Glioblastoma

Jeffrey Bacha[1], Anne Steino[1], Richard Schwartz[1], John Langlands[1], Sarath Kanekal[1], Lorena M. Lopez[1], Barbara O'Brien[2], Zhong-ping Chen[3], Dennis M. Brown[1]

[1]DelMar Pharmaceuticals, Inc., Vancouver, Canada and Menlo Park, California, USA; [2]MD Anderson Cancer Center, Houston, TX, USA; [3]Sun Yat-sen University, Guangzhou, China

ABSTRACT # ACTR-42

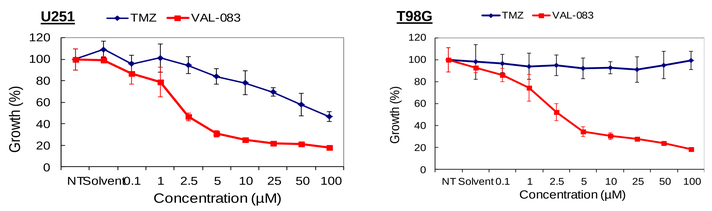
Glioblastoma (GBM) is the most common CNS-tumor. Patients with recurrent GBM have few treatment options and dismal prognosis. O^6-methylguanine-DNA-methyltransferase (MGMT) is correlated with resistance to standard-of-care treatment with temozolomide and poor patient outcomes. Dianhydrogalactitol (VAL-083) is a bi-functional alkylating agent that readily crosses the blood-brain barrier and has demonstrated MGMT-independent activity in multiple GBM cell-lines and cancer stem cells, *in vitro*. VAL-083 showed promise against CNS-tumors in prior NCI-sponsored clinical trials. We recently concluded a phase I/II clinical trial studying VAL-083 in recurrent GBM after failing temozolomide and bevacizumab, suggesting potential of VAL-083 to offer clinically meaningful survival benefits and a promising new treatment for GBM patients who have failed or are unlikely to respond to currently available chemotherapeutic regimens. In this phase I/II trial, **VAL-083, 40 mg/m²/day x 3 every 21 days** was well-tolerated and was selected for study in subsequent clinical trials in GBM. These trials include i) a pivotal, randomized Phase 3 study measuring survival outcomes compared to "physician's 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 bevacizumab-failed GBM. ii) A single-arm, biomarker-driven, Phase 2 study to determine if treatment of MGMT-unmethylated recurrent GBM with VAL-083 improves overall survival at 9 months, compared to historical control in bevacizumab-naïve patients (clinicaltrials.gov identifier: NCT02717962). iii) A single arm Phase 2 study to confirm the tolerability of DelMar's dosing regimen in combination with radiotherapy and to explore the activity of VAL-083 in newly diagnosed MGMT-unmethylated GBM patients whose tumors are known to express high MGMT levels. The results of these studies may support a new treatment paradigm in chemotherapeutic regimens for the treatment of GBM.

Background & Historical Clinical Data

TABLE 1: Historical data comparing randomized clinical trials of VAL-083 versus other chemotherapies used in the treatment of GBM. Reported median survival of VAL-083 in combination with radiotherapy, and the benefit versus radiotherapy alone is similar or superior to other alkylating agents.

XRT +	VAL-083 *(Eagan 1979)[1]*	TMZ *(Stupp 2005)*	Nitrosourea therapy		
			BCNU *(Walker 1976)*	CCNU *(Reagan 1976)*	ACNU *(Walker 1976)*
Median survival (months)	16.8	14.6	12.5	13.0	8.8
Benefit vs. XRT alone	8.4	2.5	2.5	1.2	n/a

DelMar Pharmaceuticals Data Demonstrates that VAL-083 Activity is Independent of MGMT-mediated Resistance



GBM Cell Line1		U251	T98G
MGMT promoter methylation		Methylated (low expression)	Unmethylated (high expression)
IC_{50}	VAL-083	2.5μM	2.5μM
	TMZ	10.0μM	>>100μM

FIGURE 1. TMZ vs. VAL-083 in Adult GBM Cell Lines (3000 cells/well, 72-h exposure)[5]

Summary of DelMar Pharmaceuticals Phase I/II Clinical Trial Results in Recurrent GBM Patients Following Bevacizumab Failure Compared to Published Trials[6]

TABLE 2. Patients receiving an assumed therapeutic dose of VAL-083 (20 - 40mg/m²) suggests that VAL-083 may offer improved survival for GBM patients following bevacizumab failure in comparison to published results.

Reference	Post Bevacizumab Salvage Therapy	Median Survival from Bevacizumab Failure
Rahman (2014)[7]	nitrosourea	4.3 months
Mikkelsen (2011)[8]	TMZ + irinotecan	4.5 months
Lu (2011)[9]	dasatinib	2.6 months
Reardon (2011)[10]	etoposide	4.7 months
Reardon (2011)[10]	TMZ	2.9 months
Iwamoto (2009)[11]	various	5.1 months
DLM-10-001 (2016)[6]	***VAL-083 (n=22)***	***8.35 months***

TABLE 3. VAL-083 Safety Observations in DelMar Pharmaceuticals Phase I/II Clinical Trial

Hematologic parameter and CTCAE grade	dose n =	≤30 mg/m² 20	40 mg/m² 17	45 mg/m² 4	50 mg/m² 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

CONCLUSIONS & NEXT STEPS

- ✓ **VAL-083 is a "first-in-class" alkylating agent with demonstrated activity against GBM in historical-NCI sponsored clinical trials.**
- ✓ **DelMar Pharmaceuticals has demonstrated that VAL-083's unique cytotoxic mechanism maintains activity against GBM cell lines independent of MGMT-mediated repair *in vitro.***
- ✓ **A modernized dosing regimen of 40 mg/m²/day VAL-083 administered on the first three days of a three week cycle was found to be well-tolerated in bevacizumab-failed GBM patients; and has been selected by DelMar Pharmaceuticals for further study in subsequent clinical trials.**
- ✓ **Results of a recent single-arm open label trial support the potential of VAL-083 to offer a clinically meaningful survival benefit in the post-bevacizumab GBM population, but must be further validated in a randomized clinical trial.**

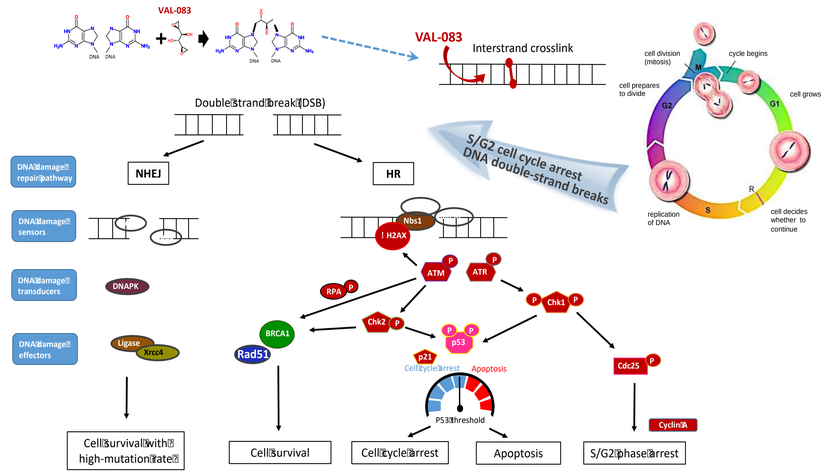
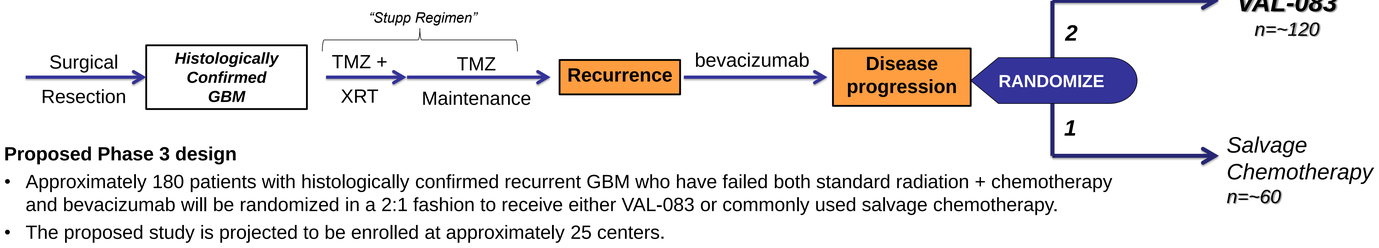


FIGURE 2. VAL-083 induces interstrand crosslink leading to double-strand breaks, S/G2 phase arrest and HR activation. Red color signifies demonstrated activation/expression after VAL-083 treatment.

THREE ADDITIONAL GBM CLINICAL TRIALS ARE PLANNED:

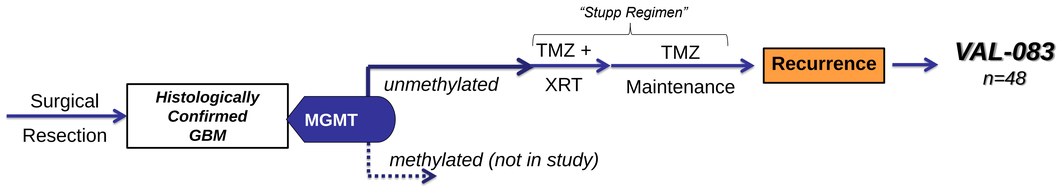
1. *A pivotal, randomized multi-center Phase 3 study measuring survival outcomes compared to a "physicians' choice" control for the treatment of bevacizumab-failed GBM.*



Proposed Phase 3 design

- Approximately 180 patients with histologically confirmed recurrent GBM who have failed both standard radiation + chemotherapy and bevacizumab will be randomized in a 2:1 fashion to receive either VAL-083 or commonly used salvage chemotherapy.
- The proposed study is projected to be enrolled at approximately 25 centers.
- The proposed primary endpoint is overall survival (OS).
- The proposed statistical design between the two arms of the study is 90% power, and is proposed to include an interim analysis at 50% events for futility with O'Brien-Fleming superiority boundary and non-binding, gamma(-5) futility boundary.
- The estimated length of the proposed study is less than 2 years from initiation.
- ***The proposed trial design is subject to feedback from FDA and other regulatory authorities .***

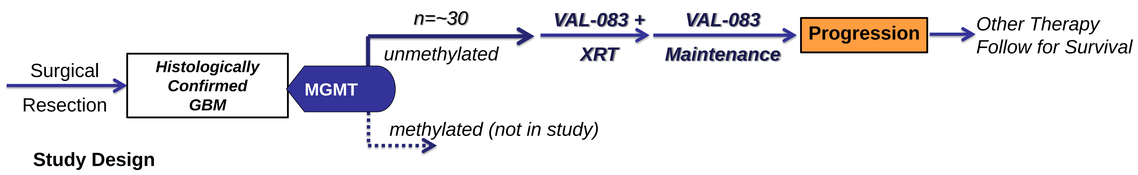
2. *An open label, single-arm, biomarker-driven, Phase 2 study of VAL-083 in patients with MGMT-unmethylated, bevacizumab-naïve recurrent GBM (clinicaltrials.gov identifier: NCT02717962)*



Study Design

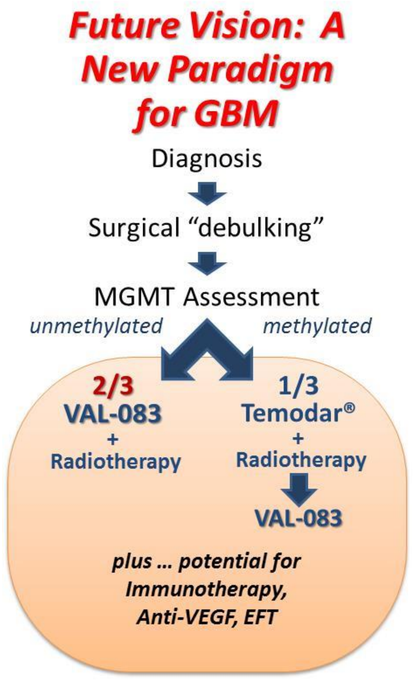
- This single arm, biomarker-driven study will enroll 48 patients to determine if treatment of MGMT-unmethylated recurrent glioblastoma with **VAL-083** improves overall survival (OS), compared to historical control.
- The lomustine arm of the recently published EORTC26101 trial will serve as the reference control.
- The study is initially being enrolled at the University of Texas MD Anderson Cancer Center as a single center trial, but may be expanded to include additional centers.

3. *An open label, single-arm, biomarker-driven, Phase 2 study of VAL-083 and radiation therapy patients with in newly diagnosed MGMT-Unmethylated GBM*



Study Design

- This single-arm trial will enroll up to 30 newly diagnosed (temozolomide-naïve) GBM patients to examine whether VAL-083 is active in patients with newly diagnosed GBM with unmethylated-MGMT compared to historical control. This information is intended to lead to a global randomized Phase II/III clinical trial evaluating the efficacy of VAL-083 in newly diagnosed GBM patients with unmethylated-MGMT.
- Progression free survival (PFS) will serve as the primary endpoint to assess VAL-083 treatment activity.
- The study will also confirm the safety and tolerability of VAL-083 in combination with a standard-of-care radiation regimen.
- The study will initially be enrolled at the Sun-Yat Sen University (Guangzhou, China) as a single center trial, but may be expanded to include additional centers.



References:

1. ***Eagan et al. JAMA***. *1979; 241(19):2046-50*
2. ***Stupp et al.*** *N Engl J Med 2005; 352(10):997-1003*
3. ***Walker et al.*** *Cancer Treat Rep 60:713-716 (1976)*
4. ***Reagan et al.*** *J. Neurosurg 44:186-190 (1976)*
5. ***Hu et al.*** *AACR annual meeting 2012*
6. ***ClinicalTrials.gov.*** *NCT01478178*
7. ***Rahman et al.*** *Neuro Oncol. 2014; 16(11):1523-9*
8. ***Mikkelsen et al.*** *Neuro Oncol 2011; 13(1): 143-51*
9. ***Lu et al.*** *J neuro Oncol 2011;104(1):287-91*
10. ***Reardon et al.*** *J Neuro Oncol. 2011; 103(2):371-9*
11. ***Iwamoto et al.*** *Neurology 2009; 73(15):1200-1206*