Clinical trials of VAL-083 in patients with chemo-resistant glioblastoma

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

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

ABSTRACT #TPS2082

Glioblastoma (GBM) is the most common and aggressive primary brain cancer. Current standard of care includes surgery, radiation and treatment with temozolomide (TMZ), however nearly all tumors recur and the prognosis for recurrent GBM is dismal. Most GBM tumors have unmethylated promoter status for O^6-methylguanine-DNA-methyltransferase (MGMT); a validated biomarker for TMZ-resistance. Second-line treatment with anti-angiogenic agent bevacizumab has not improved overall survival (OS) and 5-year survival is less than 3%. Dianhydrogalactitol (VAL-083) is a bi-functional alkylating agent targeting N7-Guanine and inducing interstrand DNA cross-links, double-strand breaks and cell death in GBM cell lines and GBM cancer stem cells, independent of MGMT status *in vitro*. VAL-083 readily crosses the blood-brain barrier and accumulates in brain tumor tissue. Our recent phase I/II clinical trial in recurrent GBM patients failing both TMZ and bevacizumab, suggested that VAL-083 offers clinically meaningful survival benefits for patients with recurrent GBM and pinpointed a new dosing regimen (40 mg/m^2/d on days 1,2,3 of a 21-day cycle) which was well-tolerated and was selected for study in subsequent GBM trials. These trials include i) an ongoing open-label, single-arm, biomarker driven, Phase 2 study to determine if VAL-083 treatment of *MGMT*-unmethylated adult GBM patients at first recurrence/progression, prior to bevacizumab improves overall survival at 9 months, compared to lomustine in the recently published EORTC26101 trial (clinicaltrials.gov identifier: NCT02717962). ii) ***Phase 3 Study in Temozolomide-Avastin Recurrent GBM ("STAR-3"):*** A pivotal Phase 3 study in recurrent GBM after failing both TMZ and bevacizumab. The control arm will consist of a limited number of salvage chemotherapies currently used in bevacizumab-failed GBM. If successful, this study will serve as the basis for a New Drug Application (NDA) submission for VAL-083. iii) A single arm, biomarker driven, Phase 2 study to confirm the tolerability and efficacy of VAL-083 in combination with radiotherapy 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

Dianhydrogalactitol (VAL-083) is a bi-functional DNA targeting agent with a distinct mechanism-of-action differentiating it from other chemotherapeutic agents used in the treatment of GBM and other CNS tumors. VAL-083 readily crosses the blood-brain barrier and accumulates in brain tumor tissue. VAL-083 targets N7 of guanine and has demonstrated **MGMT-independent cytotoxicity** in multiple GBM cell-lines and cancer stem cells and is able to overcome temozolomide-resistance *in vitro* demonstrating a distinct mechanism of action.

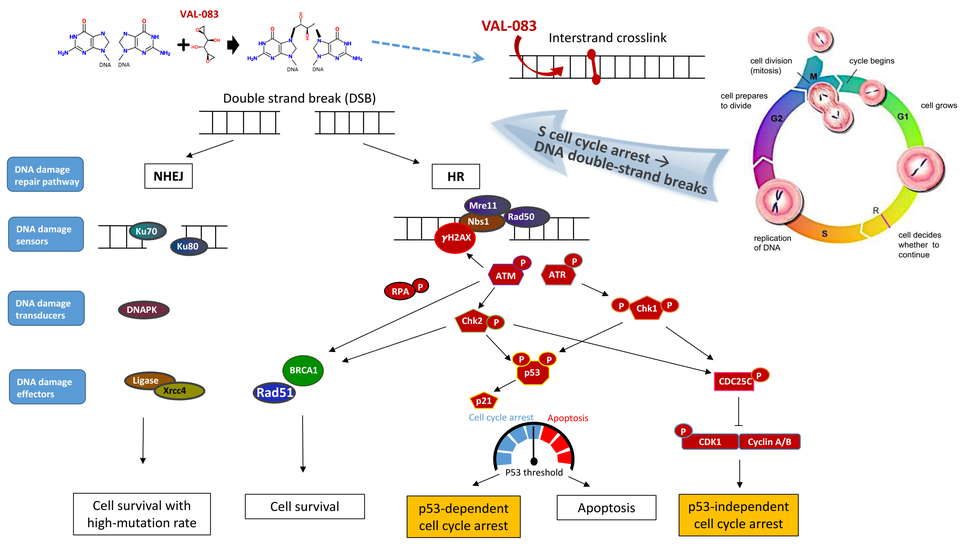


FIGURE 1. VAL-083 induces interstrand crosslinks at N7 guanines leading to double-strand breaks and HR activation independent of MGMT, and mediating cell cycle arrest through p53-dependent and p53-independent pathways[7,14]. Red color signifies demonstrated activation/expression after VAL-083 treatment.

Historical Clinical Data

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

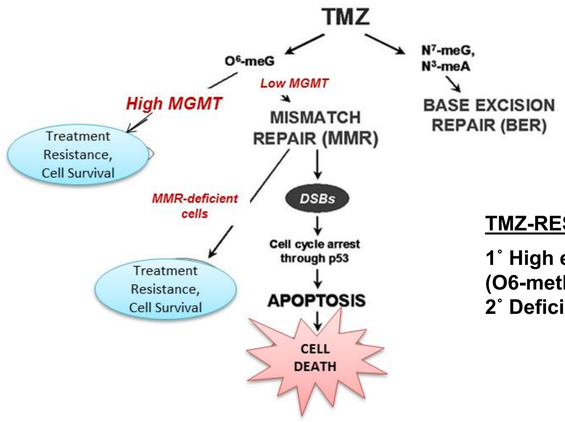
			Nitrosourea therapy		
XRT +	VAL-083 *(Eagan 1979)*[1]	TMZ *(Stupp 2005)*[2]	BCNU *(Walker 1976)*[3]	CCNU *(Reagan 1976)*[4]	ACNU *(Takakura 1986)*[5]
Median survival (months)	16.8	14.6	12.5	13.0	8.8
Benefit vs. XRT alone	***8.4***	*2.5*	*2.5*	*1.2*	*n/a*

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/m^2) 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)[9]	nitrosourea	4.3 months
Mikkelsen (2011)[10]	TMZ + irinotecan	4.5 months
Lu (2011)[11]	dasatinib	2.6 months
Reardon (2011)[12]	etoposide	4.7 months
Reardon (2011)[12]	TMZ	2.9 months
Iwamoto (2009)[13]	various	5.1 months
DLM-10-001 (2016)[6]	***VAL-083 (n=22)***	***8.4 months***

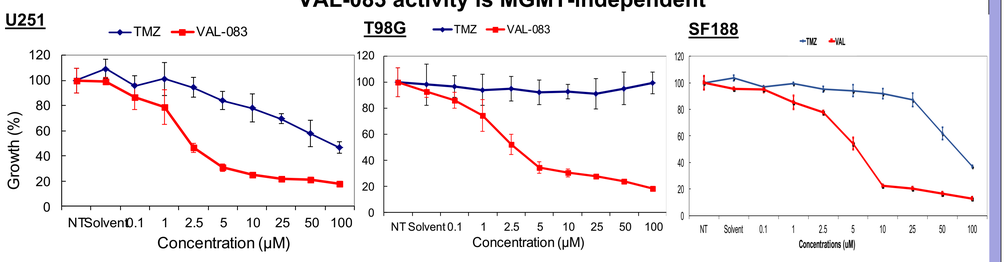
TMZ DUAL MECHANSMS OF RESISTANCE: MGMT & MMR



TMZ-RESISTANCE MECHANISMS

1˚ High expression of MGMT (O6-methylguanine DNA methyltransferase)
2˚ Deficient MMR (mismatch repair) system

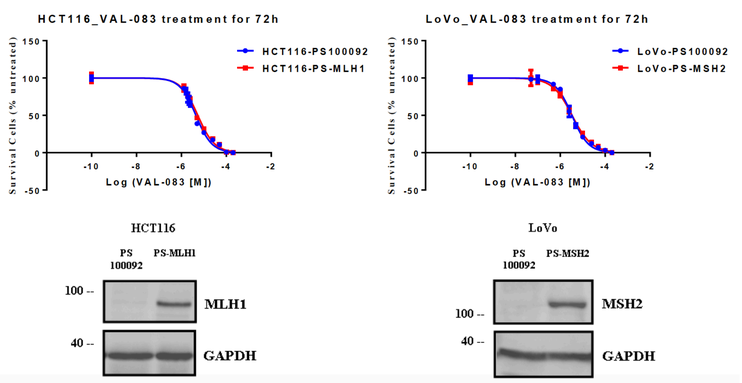
VAL-083 activity is MGMT-independent



GBM Cell Line1	***U251***	***T98G***	***SF188***
MGMT promoter methylation	Methylated (low expression)	Unmethylated (high expression)	Methylated (low expression)
IC_{50} VAL-083	2.5μM	2.5μM	4.5
IC_{50} TMZ	10.0μM	>>100μM	710

FIGURE 2. Effect of TMZ vs. VAL-083 in Adult GBM Cell Lines (3000 cells/well, 72-h exposure)[7]

VAL-083 activity is MMR-independent



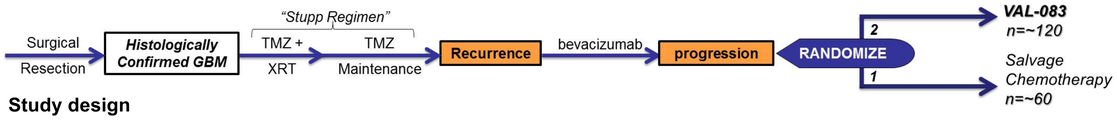
VAL-083 activity against colorectal cancer cell lines was independent of MMR: Cytotoxicity of VAL-083 measured in two pairs of isogenic human colorectal cancer cell lines. MMR-proficient cell lines: HCT116-PS-MLH1 and LoVo-PS-MSH2, were established by lentiviral infection. MMR-deficient cell lines: LoVo-PS100092 (MSH2-deficient cell line) and LoVo-PS-MSH2 (MSH2-proficient cell line). N=3

CONCLUSIONS & NEXT STEPS

- ✓ **VAL-083 is a "first-in-class" DNA targeting agent with demonstrated activity against GBM in historical-NCI sponsored clinical trials.**
- ✓ **VAL-083's unique cytotoxic mechanism maintains activity against GBM cell lines and cancer stem cells independent of MGMT methylation and MMR *in vitro*.**
- ✓ **A dosing regimen of 40 mg/m^2/day VAL-083 administered on days 1,2,3 of a 21-day cycle was well-tolerated and data supports the potential to offer a clinically meaningful survival benefit in bevacizumab failed GBM patients**
- ✓ **Taken together, these data support the potential of VAL-083 to offer a new treatment option for GBM patients whose tumors exhibit features correlated with resistance to currently available therapies.**

Three additional clinical trials with VAL-083 are planned or enrolling

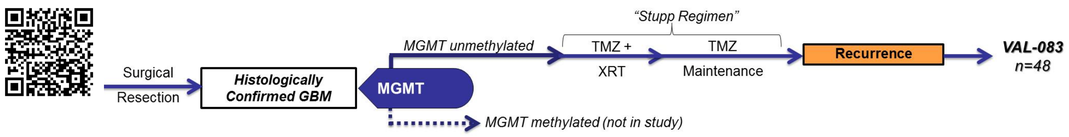
1. Phase 3 Study in Temozolomide-Avastin Recurrent GBM ("STAR-3"): A pivotal randomized, controlled trial of VAL-083 in patients with recurrent GBM who have failed temozolomide/radiation therapy and bevacizumab (clinicaltrials.gov identifier: NCT03149575)



Study 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 in the United States.
- The proposed primary endpoint is overall survival (OS).
- The estimated length of the proposed study is less than 2 years from initiation.
- ***STATUS: Study start-up activities underway in the United States***

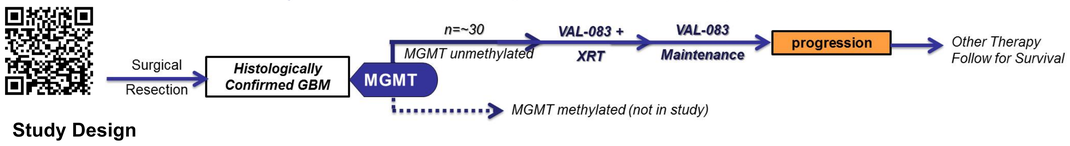
2. Open label, single-arm, biomarker-driven Phase 2 trial in MGMT-unmethylated, bevacizumab-naïve, recurrent GBM is currently enrolling at MD Anderson Cancer Center (clinicaltrials.gov identifier: NCT02717962)



Study Design

- 48 patients will be enrolled to determine if treatment of MGMT-unmethylated recurrent GBM 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[13].
- ***STATUS: Currently enrolling at the University of Texas MD Anderson Cancer Center***

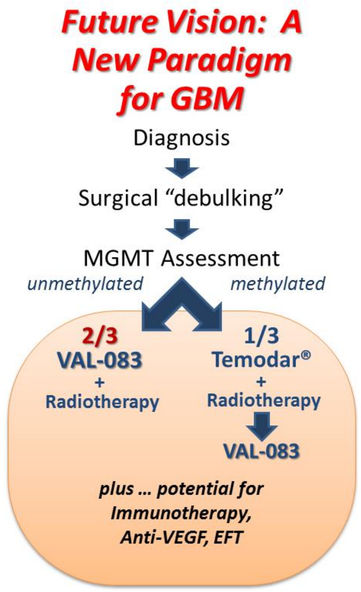
3. Open label, single-arm, biomarker-driven, Phase 2 trial of VAL-083 and radiation therapy in newly diagnosed MGMT-Unmethylated GBM (clinicaltrials.gov identifier: NCT03050736)



Study Design

- Up to 30 patients with newly diagnosed GBM with unmethylated-MGMT will be treated with VAL-083 and compared to historical control; the results will support a global randomized Phase II/III clinical trial evaluating VAL-083 efficacy in newly diagnosed GBM patients with unmethylated-MGMT.
- Progression free survival (PFS) will serve as the primary endpoint to assess VAL-083 treatment activity.
- ***STATUS: Study start-up activities underway at Sun Yat Sen University Cancer Center (Guangzhou, China)***

Future Vision: A New Paradigm for GBM



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