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

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ABSTRACT #09.57

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.

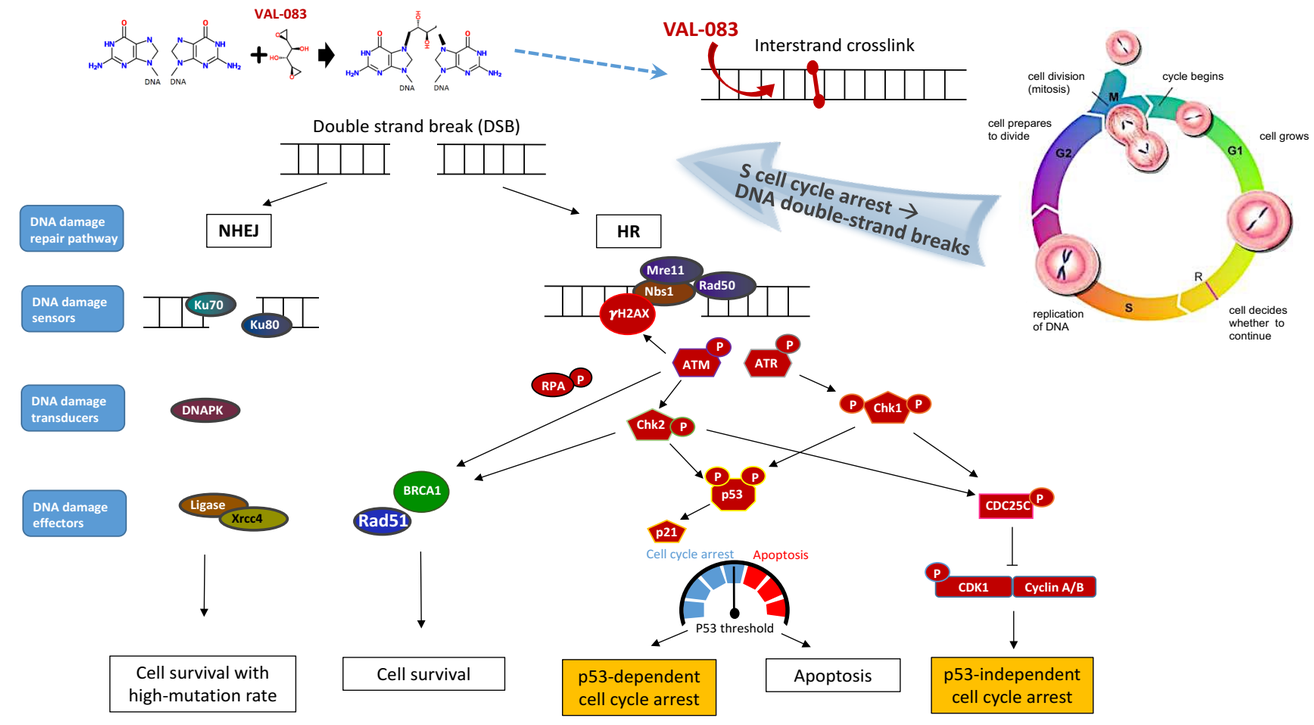


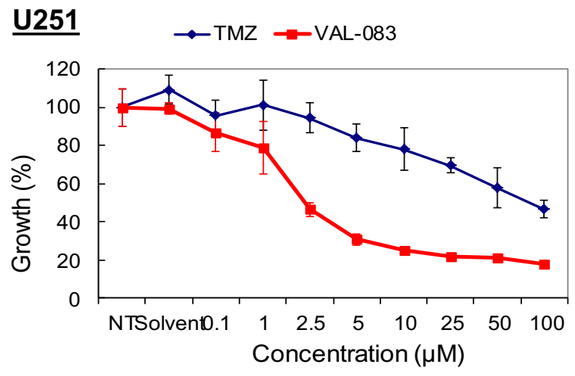
FIGURE 1. VAL-083 induces interstrand crosslinks at N7 guanines leading to double-strand breaks and HR activation independent of MGMT, and mediating cell cycle arrest through p53-dependent and p53-independent pathways[5,12]. Red color signifies demonstrated activation/expression after VAL-083 treatment.

Historical Clinical Data

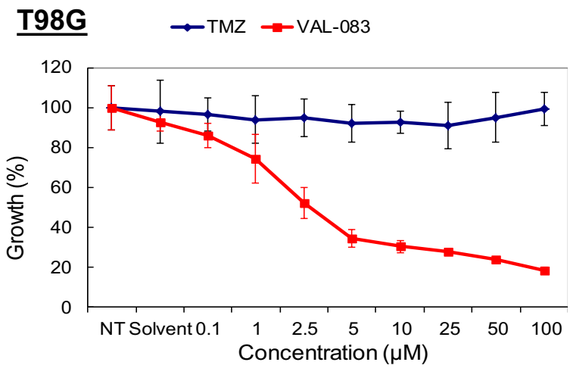
TABLE 1: Historical data comparing randomized clinical trials of VAL-083 versus other chemotherapies used in the treatment of GBM. Reported median survival of VAL-083 in combination with radiotherapy, and the benefit versus radiotherapy alone is similar or superior to other alkylating agents.

XRT +	VAL-083 *(Eagan 1979)*[1]	TMZ *(Stupp 2005)*[2]	Nitrosourea therapy		
			BCNU *(Walker 1976)*[3]	CCNU *(Reagan 1976)*[4]	ACNU *(Walker 1976)*[3]
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*

U251



T98G



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 2. Effect of 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/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)[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***

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 status *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.**

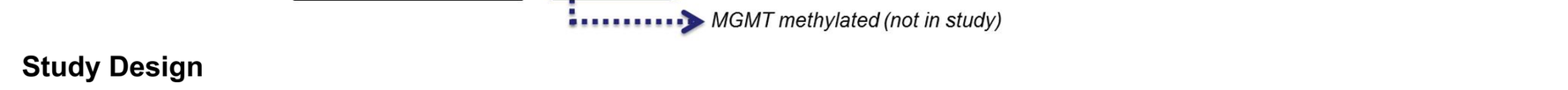
Three additional clinical trials with VAL-083 are planned or enrolling

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.

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***

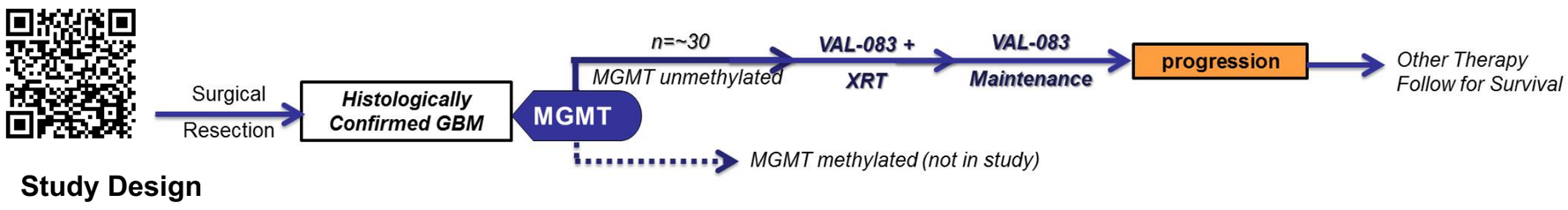
2. Open label, single-arm, biomarker-driven Phase 2 trial in MGMT-unmethylated, bevacizumab-naïve, recurrent GBM is currently enrolling at MD Anderson Cancer Center *(clinicaltrials.gov identifier: NCT02717962)*



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***

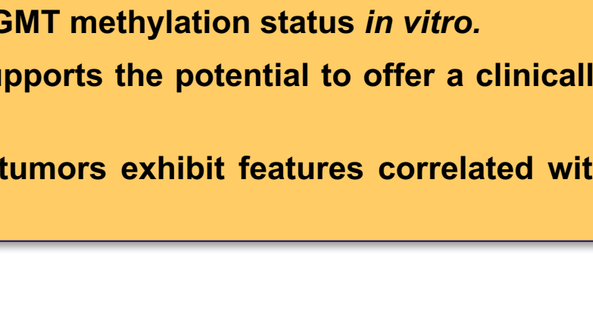
3. Open label, single-arm, biomarker-driven, Phase 2 trial of VAL-083 and radiation therapy in newly diagnosed MGMT-Unmethylated GBM *(clinicaltrials.gov identifier: NCT03050736)*



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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