An open-label, biomarker driven, Phase 1/2 study of dianhydrogalactitol (VAL-083) with radiation therapy in patients with newly diagnosed MGMT-unmethylated GBM

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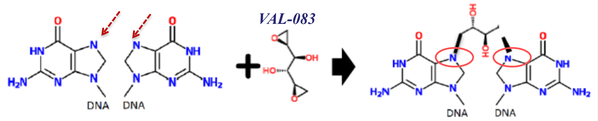
Glioblastoma (GBM) is the most common and aggressive primary brain cancer. Current standard-of-care includes surgery followed by concomitant chemo-radiation and adjuvant temozolomide (TMZ). Unmethylated promoter status for O^6-methylguanine-DNA-methyltransferase (MGMT), a validated biomarker for TMZ-resistance, is strongly correlated with TMZ-resistance. In addition, defective DNA mismatch repair (MMR) has been identified as a secondary mechanism of TMZ-resistance. MGMT-unmethylated tumors represent a majority of newly diagnosed GBM patients demonstrating significantly inferior progression free and overall survival compared to MGMT-methylated GBM patients.

VAL-083 overcomes MGMT-mediated chemoresistance

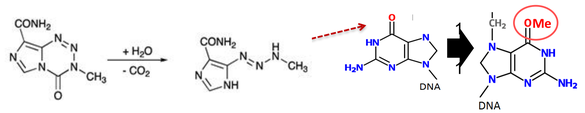
VAL-083 is a novel bi-functional DNA targeting agent that rapidly induces interstrand cross-links at N^7-guanine, leading to DNA double-strand breaks (DSBs) and ultimately cell death. The N^7-targeting mechanism differs from TMZ and nitrosoureas, enabling VAL-083 to overcome MGMT-mediated chemoresistance.

Mechanism of VAL-083 via crosslinks at N^7 of guanine



2 guanine bases on DNA — *VAL-083 – interstrand crosslink (ICL)*

Mechanism of temozolomide via alkylation at O^6 of guanine



Temozolomide converts to active state (MTIC) at physiological pH — *Alkylation of O^6 guanine*

FIGURE 1. *The N^7-targeting mechanism of action of VAL-083 differs from those of O6-alkylating agents like temozolomide and nitrosoureas.*

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)
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6. Fouse S, et al. Neuro-Oncology 16 (2014)

VAL-083 COMBINATION WITH RADIATION THERAPY PROVIDED SIMILAR OR SUPERIOR CLINICAL BENEFIT COMPARED TO OTHER CHEMOTHERAPIES IN HIGH GRADE GLIOMAS

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[1]	TMZ[2]	BCNU[3]	CCNU	ACNU[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*

VAL-083 POTENTIATES RADIATION AND IS ACTIVE AGAINST GBM CANCER STEM CELLS, INDEPENDENDENT OF MGMT

VAL-083 (5 μM) overcame TMZ-resistance in both GBM cancer cells and GBM cancer stem cells (CSCs) independent of MGMT (Figure 1A,B). In addition, when VAL-083 was added to TMZ-resistant CSC cultures at low micromolar doses (1μM) with or without 2Gy radiation, VAL-083 acted as a radio-sensitizer against CSC's (Figure 1C).

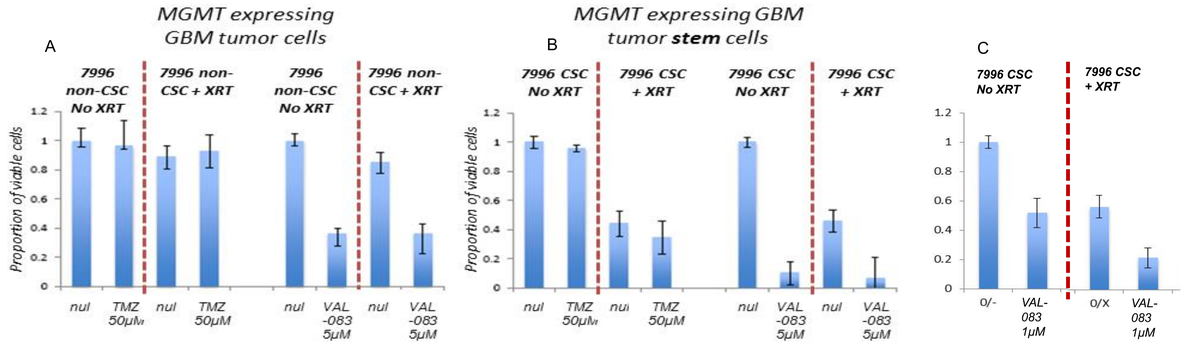
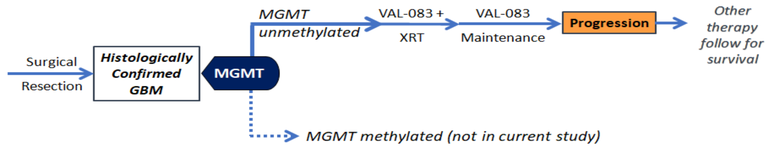


FIGURE 2. *Cell viability for paired non-CSC (A) and CSC (B,C) GBM cultures. MGMT expressing SF7996 CSCs and non-CSCs were treated with TMZ (50 μM) or VAL-083 (1 or 5 μM) on days 1,2 and 3 either with or without radiation (2Gy) and analyzed for cell viability 6 days post treatment.[6]*

An open label, single-arm, biomarker-driven, Phase 1/2 study of VAL-083 and radiation therapy in patients with newly diagnosed MGMT-unmethylated GBM. Currently enrolling at Sun Yat-Sen University Cancer Center

(Clinicaltrials.gov identifier NCT03050736)

STUDY DESIGN



- Up to 30 patients with newly diagnosed GBM with unmethylated-MGMT will be treated with VAL-083 IV on days 1,2,3 of a 21 day cycle combined with radiotherapy (2Gy/day x 5 days) for 6 weeks followed by 24 weeks of VAL-083 maintenance therapy.
- The study is being conducted in two parts:
  1) *Dose-confirmation:* VAL-083 in cohorts (20,30 and 40 mg/m^2/day IV) to assess safety and activity when administered concurrently with XRT to confirm the maximum tolerated dose (MTD). A dose escalation scheme will be followed if dose-limiting toxicity (DLT) is observed in any of the cohorts.
  2) *Expansion:* VAL-083 will be studied in up to 20 additional patients at the target dose of 40mg/m^2 VAL-083 administered concurrently with XRT.

Tumor response will be assessed by MRI, according to RANO criteria.

- Progression free survival (PFS) will serve as the primary endpoint.
- Secondary endpoints include overall survival (OS), pharmacokinetic assessments of plasma and CSF samples (when available) and safety and tolerability evaluations of VAL-083 in combination with a standard-of-care radiation regimen.

STUDY STATUS *(31-Mar/2018)*

- **Dose-escalation, studying 20 and 30 mg/m^2/day cycles, has been completed (4 patients enrolled)**
- **No DLTs reported after treatment with multiple cycles of VAL-083**
- **The next patient enrolled will receive the study target dose of 40 mg/m^2/day VAL-083 combined with radiation**

View trial details (http://clinicaltrials.gov):