Phase 2 study of dianhydrogalactitol (VAL-083) with radiation therapy in patients with newly diagnosed, *MGMT*-unmethylated glioblastoma

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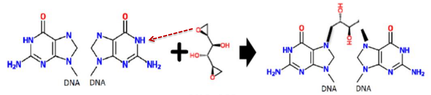
ABSTRACT #CT116

Glioblastoma (GBM) is the most common and aggressive primary brain cancer. Current standard-of-care includes surgery followed by chemo-radiation and temozolomide. An unmethylated promoter for O^6-methylguanine-DNA-methyltransferase (MGMT) is a validated biomarker for temozolomide-resistance and is strongly correlated with poor outcomes. Unmethylated MGMT represents the majority of newly diagnosed GBM tumors. VAL-083 is a first-in-class bi-functional DNA-targeting agent that has shown activity against GBM in NCI-sponsored clinical trials both as single agent and in combination with radiotherapy. VAL-083 induces interstrand cross-links at N^7-guanine, leading to DNA double-strand breaks and cell-death. VAL-083's unique mechanism-of-action circumvents MGMT-mediated chemoresistance, and it has demonstrated cytotoxicity in MGMT-unmethylated GBM cell-lines, cancer stem cells (CSCs) and in vivo models. Furthermore, VAL-083 acts as a radiosensitizer in GBM CSCs and non-CSCs. We completed a dose-escalation trial of VAL-083 in recurrent GBM, and a generally well-tolerated dosing regimen was selected for further clinical development. The present trial is an ongoing open-label, biomarker-driven, Phase 2 study to evaluate the tolerability and efficacy of VAL-083 in combination with radiotherapy in newly diagnosed MGMT-unmethylated GBM patients. A treatment regimen, consisting of a 6-week induction period of VAL-083 and concurrent radiation (2 Gy daily, 5 days/week) followed by up to 24 weeks of maintenance therapy with single-agent VAL-083, is being evaluated. The study is being conducted in two parts. The dose-confirmation part (20, 30, and 40 mg/m^2/day IV infusion on days 1-3 of a 21-day cycle) has been completed, and the expansion part has been initiated in up to 20 additional patients at 30 mg/m^2/day IV infusion on days 1-3 of a 21-day cycle. Tumor response will be assessed by MRI, according to RANO criteria. Efficacy endpoints include progression-free survival (PFS) and overall survival (OS). Additional endpoints include safety evaluations and pharmacokinetic assessments of plasma and CSF samples. Trial design, enrollment and safety data update will be provided at the meeting. Clinicaltrials.gov identifier: NCT03050736.

BACKGROUND

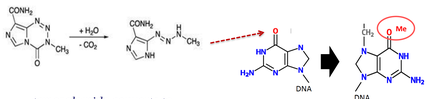
Mechanism of action of VAL-083 differs from that of temozolomide

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



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

Mechanism of temozolomide (TMZ) via alkylation at O^6 of guanine.



temozolomide converts to active state (MTIC) at physiological pH — *guanine base on DNA* — *alkylation of O^6 guanine*

Figure 1. *The N^7-targeting mechanism of action of VAL-083 differs from those of O^6-alkylating agents like temozolomide and nitrosoureas.*

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.[1] VAL-083's unique cytotoxic mechanism circumvents MGMT-mediated chemoresistance and differentiates it from other therapies used in the treatment of GBM, including TMZ.[2,3] VAL-083 is able to overcome TMZ-resistance in GBM, *in vitro* and *in vivo* and it acts as a radio-sensitizer against GBM cancer stem cells *in vitro*.[3]

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 in combination with radiotherapy, and the benefit versus radiotherapy (XRT) alone is similar or superior to other DNA-targeting agents.

			Nitrosourea therapy		
XRT +	VAL-083[4]	TMZ[5]	BCNU[6]	CCNU[7]	ACNU[8]
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*

This distinct mechanism of action of VAL-083 combined with results from historical clinical trials suggests that VAL-083 in combination with radiation therapy may offer a treatment alternative against GBM tumors with MGMT-mediated resistance to chemotherapeutic agents, including TMZ and nitrosoureas.

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STUDY UPDATE *(cut-off date Feb 15th, 2019)*

- Study currently enrolling at the Sun Yat-sen University Cancer Center;
- 15 subjects have been enrolled as of Feb 15th, 2019;
- In the dose-escalation stage, grade 3+ myelosuppression was observed in 2 of 3 patients treated at 40 mg/m^2. Therefore, rather than proceeding with a formal Maximum Tolerated Dose (MTD) assessment, the prior cohort VAL-083 dosage of 30 mg/m^2 daily x 3 every 21 days has been selected for further study;
- The study has met the goal of the dose-escalation stage, treatment is ongoing;
- Similar to prior experience, myelosuppression has been the most common adverse event (AE) observed;
- AEs generally resolved spontaneously;
- Two dose-limiting toxicities have been reported (thrombocytopenia) - one at the 40 mg/m^2/day dose and one at the 30 mg/m^2/day dose;
- Two SAEs possibly related to treatment have been observed in two study subjects to date;
- Concentrations of VAL-083 in both plasma and CSF have been determined in 7 patients;
- Preliminary data indicate the concentration of VAL-083 is generally higher in CSF than in plasma at 2 hours post-infusion.

Dose (mg/m2)	n	Mean Concentrations (ng/mL)		Conc. Ratio @ 2 hours
		Plasma (2 hours post dose)	CSF (2 hours post dose)	CSF/Plasma
20	1	110	154	1.40
30	3	97	134	1.41
40	3	170	190	1.13

Figure 2. Concentration of VAL-083 in plasma and CSF 2 hours post infusion.

- Tumor progression assessments at post-cycle 3 MRIs, based on the trial investigator's clinical and radiologic assessment, according to the Response Assessment in NeuroOncology (RANO) criteria have been completed for 11 patients:
  - five were assessed by the Principal Investigator as having a "Complete Response", three of whom were based on significant tumor shrinkage, and two of whom were based on their tumors continuing to remain "below measurable level" from post-surgery baseline MRI to post-cycle 3 MRI;
  - six patients were assessed as having "Stable Disease";
- One patient died prior to their post-cycle 3 MRI; three have not been on study long enough to reach their planned post-cycle 3 MRI;
- 12 of the 15 patients were still alive at the data cut-off.

Updated NCCN guidelines and VAL-083 with irradiation as first-line treatment for GBM

Concurrent irradiation and TMZ treatment has been established as first-line treatment for patients with newly diagnosed GBM since at least 2005. Because the efficacy of TMZ is limited for tumors with an unmethylated promoter for DNA repair protein MGMT, the NCCN guidelines for GBM were recently updated to allow the use of radiation therapy alone for those patients who are MGMT-unmethylated.[9]

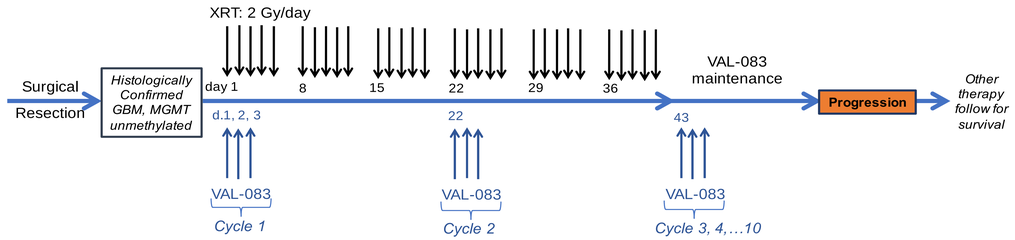
VAL-083 has been shown to act as a radio-sensitizer in MGMT-unmethylated GBM cells *in vitro* and to improve median survival compared to radiation alone in high-grade gliomas, clinically.[3,4]

CONCLUSION AND FUTURE DIRECTIONS

- The dose-escalation part of the study has been completed;
- VAL-083 at a dose of 30 mg/m^2/day was selected for combination with irradiation for the treatment of newly diagnosed GBM;
- Two dose-limiting toxicities have been reported (thrombocytopenia) - one at the 40 mg/m^2/day dose and one at the 30 mg/m^2/day dose
- VAL-083 at 30 mg/m^2 in combination with radiation therapy is generally safe and well-tolerated;
- Five of the first 12 patients were assessed as "Complete Response" and six as "Stable Disease" by the trial investigator after post-cycle 3 MRIs (one patient died prior to that time point);
- Levels of VAL-083 are generally higher in CSF compared to plasma at 2 hours post dose;
- Enrollment into the expansion stage of the study is ongoing at 30 mg/m^2/day on days 1,2 and 3 every 21 days.

STUDY DESIGN

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).*



- 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 up to 24 weeks of VAL-083 maintenance therapy;
- The study is being conducted in two stages:
  - Dose-escalation: 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 was followed if dose-limiting toxicity (DLT) is observed in any of the cohorts;
  - Expansion: VAL-083 is being studied in up to 20 additional patients at the determined maximum tolerated dose of 30 mg/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.