Poster # CT273

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

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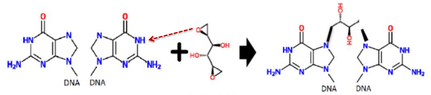
ABSTRACT #10227

Glioblastoma (GBM) is the most common and aggressive primary brain cancer. Current standard-of-care includes surgery followed by chemo-irradiation and temozolomide (TMZ). An unmethylated promoter for O^6-methylguanine DNA methyltransferase (MGMT) is a validated biomarker for TMZ-resistance and is strongly correlated with poor outcomes. The majority of glioblastoma multiforme (GBM) patients have an unmethylated MGMT promoter status, leading to limited response to TMZ and decreased survival. Dianhydrogalactitol (VAL-083) is a novel bi-functional DNA targeting agent that induces inter-strand cross-links at N^7-guanine, leading to DNA double-strand breaks and ultimately cell death. VAL-083 circumvents MGMT-mediated drug-resistance and 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. A Phase 2, open-label, biomarker-driven, study has been initiated to evaluate the tolerability and efficacy of VAL-083 in combination with radiation therapy (RT) in newly diagnosed MGMT-unmethylated GBM patients. A treatment regimen, consisting of a 6-week induction period of VAL-083 given IV at 20, 30, or 40 mg/m^2/day x 3 days every 21 days 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 has 2 stages: Stage 1 is a dose-escalation and induction format to establish a recommended dose of VAL-083 when administered concurrently with RT based on safety and tolerability. The dose escalation stage has been completed and we identified a recommended dose of 30 mg/m^2/day of VAL-083 in combination with RT as generally safe and well-tolerated. Stage 2 comprises an expansion stage to enroll up to 20 additional patients at 30 mg/m^2/day IV infusion on days 1, 2, and 3 of 21-day cycles and is currently ongoing. 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. As of 21st January 2020, 19 subjects have initiated treatment in stage 2. Clinicaltrials.gov identifier: NCT03050736.

BACKGROUND

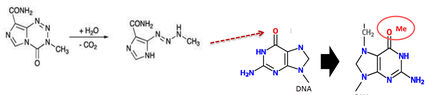
Mechanism of action of VAL-083 differs from that of temozolomide

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.[2,3,4] 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[5]	TMZ[6]	BCNU[7]	ACN[8]
Median survival (months)	15.5	14.6	11.3	12.0
Benefit vs. XRT alone	***7.4***	*2.5*	*2.8*	*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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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. Recent NCCN guidelines indicate the use of radiation therapy alone as a reasonable option for newly diagnosed patients with an unmethylated promoter for DNA repair protein MGMT, since these patients are less likely to experience clinical benefit with TMZ.[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.[3,5]

STUDY STATUS (Cut-off 15 May, 2020)

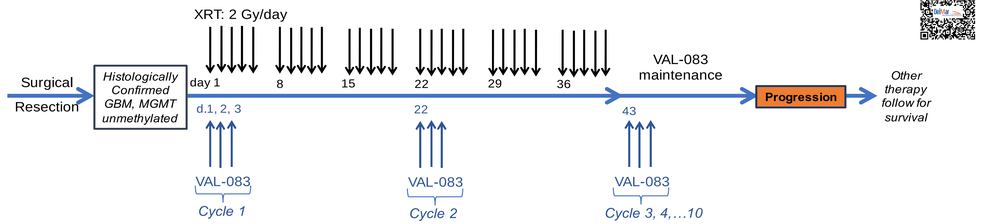
- Dose escalation cohorts evaluating doses of 20, 30 and 40 mg/m^2/day on days 1, 2 and 3 of a 21-day cycle are completed
- As myelosuppression was observed at 40 mg/m^2/day, the dose of VAL-083 was reduced to 30 mg/m^2/day on days 1, 2 and 3 every 21 days, administered concurrently with radiation therapy for the dose expansion phase of the study
- A total of 29 subjects have been treated in the study; 25 subjects have been treated with a starting dose of 30 mg/m^2/day

STUDY DESIGN

An open label, single-arm, biomarker-driven, Phase 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).*

Newly diagnosed GBM with unmethylated-MGMT are 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 8 cycles of VAL-083 maintenance therapy:

- Dose-escalation Phase : 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)
- Expansion Phase: VAL-083 is being studied in up to 20 additional patients at the determined maximum tolerated dose of 30 mg/m^2/day VAL-083 administered concurrently with XRT.
- Primary endpoint will be progression free survival (PFS) compared to historical control of TMZ at 6.9 months (Tanguturi et al, 2017)[10]. Tumor response will be assessed by MRI, according to RANO criteria
- 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



SAFETY

- Consistent with prior studies, myelosuppression has been the most common adverse event
- Hematological adverse events generally resolved spontaneously
- Serious adverse events possibly related to VAL-083 have been reported in 3/29 (10.3%) of subjects
- Three (3/29; 10.6%) DLTs have been reported in subjects who completed the first 2 cycles of treatment – 1/3 (33%) at 40 mg/m2/d starting dose; 2/25 (8%) (1 non-hematological) at 30 mg/m^2/d starting dose.

PHARMACOKINETICS

- Pharmacokinetic profiles have been determined on day 1 of cycle 1 for each subject
- Cmax and AUC are broadly linear with respect to dose; T1/2 = 0.8 hr
- Preliminary data indicate that overall the concentration of VAL-083 are generally at least as high in CSF as in plasma at 2 hours post-infusion

Table 2: Concentration of VAL-083 in Plasma and CSF

		Mean VAL-083 (SD) Conc. (ng/mL)				
Dose (mg/m^2/d)	N	Plasma C_{max}	N	Plasma 2 hr post dose	CSF 2 hr post dose	Ratio @ 2 hr CSF/Plasma
20	1	481.0	1	110.0	154	1.40
30	25	746.2 (149.4)	6	107.84 (16.65)	127.09 (26.24)	1.24 (0.35)
40	3	898.7 (69.6)	3	169.7 (41.9)	189.67 (69.89)	1.13 (0.41)

PROGRESSION FREE SURVIVAL AND SURVIVAL

Table 3: Snapshot Median Progression Free Survival (PFS) and Survival (censored at last know date or no disease progression or known alive) from Diagnosis (Grade IV); data cut-off 15 May, 2020.

	Tanguturi et al, 2017[9]	Starting Dose of VAL-083			
		Overall	20 mg/m^2/d	30 mg/m^2/d	40 mg/m^2/d
Median PFS (months) (95%CI)	6.9 (5.0-12.5)	8.7 (6.4-11.2)	3.0 (-)	8.7 (6.0-12.0)	9.9 (9.3-9.9)
Number Progressed (%)	-	20/29 (68.9%)	1/1 (100%)	17/25 (68%)	2/3 (66.7%)
Number of deaths (%)	-	11/29 (37.9%)	1/1 (100%)	10/25 (40.0%)	0/3 (0%)

Median number of cycles of VAL-083 received for subjects (30 mg/m^2/d VAL-083) was 8.0 (range 2-13 cycles); 11 subjects received ≥ 10 cycles

CONCLUSION AND FUTURE DIRECTIONS

- VAL-083 at a dose of 30 mg/m^2/day was selected for combination with irradiation for the treatment of newly diagnosed GBM;
- The study is fully enrolled with a total of 29 subjects (25 subjects receiving 30 mg/m^2 VAL-083 as a starting dose);
- Treatment and follow-up of patients is ongoing;
- Two hematological dose-limiting toxicities have been reported (thrombocytopenia);
- VAL-083 at 30 mg/m^2 in combination with radiation therapy is generally safe and well-tolerated;
- Levels of VAL-083 are generally higher in CSF compared to plasma at 2 hours post dose;
- VAL-083 at the dose of 30 mg/m^2/d, selected for continued study, in combination with radiotherapy has demonstrated benefit with respect to disease PFS over standard of care TMZ (6.9 months – Tanguturi et al, 2017)[10] in the same setting.