Phase 2 Clinical Trial of VAL-083 in Newly Diagnosed MGMT-unmethylated GBM

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ABSTRACT # CTNI-76

Approximately 60% of glioblastoma multiforme (GBM) patients possess an unmethylated methylguanine DNA-methyltransferase (MGMT) promoter region, which confers a limited response to standard-of-care treatment with temozolomide (TMZ), resulting in shorter median survival when compared to patients with methylated MGMT promoter. 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 TMZ resistance *in vitro* and *in vivo*. A Phase 2 study has been initiated for VAL-083 in newly diagnosed MGMT unmethylated GBM. The study has 2 stages: Stage 1 is a dose-escalation safety and tolerability phase to confirm the phase 2 dose of VAL-083 when administered concurrently with radiation therapy (RT). Patients received VAL-083 at 20, 30, or 40 mg/m^2/day x 3 days every 21 days along with standard radiation treatment (RT) (2 Gy/day, 5 days/week). The dose escalation stage is complete, and 30 mg/m^2/day of VAL-083 in combination with RT was generally safe and well-tolerated. Stage 2 comprises an expansion phase to enroll up to 20 additional patients at the 30 mg/m^2/day of VAL-083 in combination with RT. As of June 2, 2020, all patients have been enrolled, with a total of 29 patients in the study, and 25 patients receiving 30 mg/m^2/day VAL-083. Of the 29 patients enrolled, 27 have completed their prospectively planned MRI scans and had their initial assessment for tumor response. Two additional patients died prior to their post-cycle 3 MRI. Consistent with our prior experience, myelosuppression was the most common adverse event. Three patients have experienced dose-limiting toxicities - one (1/3; 33%) at the 40 mg/m^2/day and two (2/25; 8%) at the 30 mg/m^2/day dose. Further safety and efficacy updates will be presented at the meeting. Clinicaltrials.gov identifier: NCT03050736.

BACKGROUND

VAL-083 is a novel bi-functional DNA targeting agent that rapidly induces interstrand cross-links at N7-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 radiosensitizer against GBM cancer stem cells *in vitro*.[3]

Reported median survival in combination with radiotherapy, and the benefit versus radiotherapy (XRT) alone is similar or superior to other DNA-targeting agents (see Table 1).

Table 1. **Historical data comparing randomized clinical trials of VAL-083 versus other chemotherapies used in the treatment of high-grade gliomas**

			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.

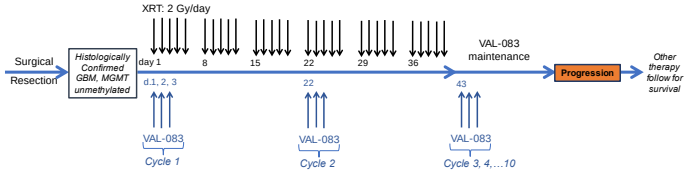
STUDY STATUS

As of the cut-off date of October 21, 2020:

- This study has been fully enrolled.
- 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 patients have been treated in the study: 1 patient received starting dose of 20 mg/m^2/day, 25 patients received a starting dose of 30 mg/m^2/day; 3 patients received a starting dose of 40 mg/m^2/day.
- As of October 22, 2020, one patient (30 mg/m^2/day) remained on treatment on VAL-083.

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. Ongoing study (enrollment completed) 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 references of TMZ at 5.3 months[9] and 6.9 months[10]. Tumor response will be assessed by MRI, according to RANO criteria
- Secondary endpoints include overall survival (OS), PK assessments of plasma and CSF, and safety and tolerability evaluations of VAL-083 in combination with a standard-of-care radiation regimen

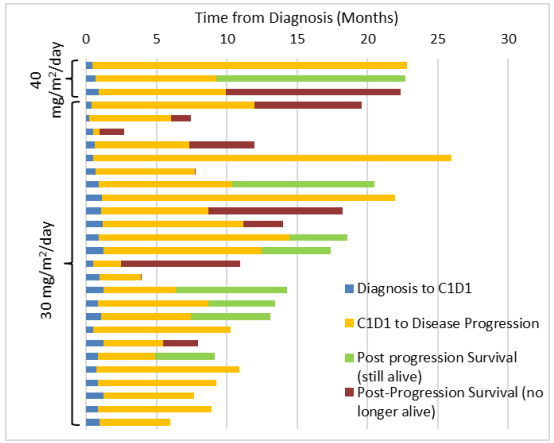


Figure 1. Disposition (cut-off date October 21, 2020) for patients who received either 40 or 30 mg/m^2/day VAL-083 as a starting dose.

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/m^2/d starting dose; 2/25 (8%) (1 non-hematological) at 30 mg/m^2/d starting dose

PHARMACOKINETICS

- Pharmacokinetic profiles determined on day 1 of cycle 1 indicate Cmax and AUC are broadly linear with respect to dose and t1/2 = 0.82 (±0.2) hr, consistent with prior studies
- At 30 mg/m^2: Cmax was 746.2 (±149.4) ng/mL; AUC was 853.2 (±305.3) ng.hr/mL; The concentration of VAL-083 is as high in CSF (127.1 ±26.2 ng/mL) as in plasma (107.8 ±16.6 ng/mL) at 2 hours post-infusion, confirming exposure to the brain.

EFFICACY

Progression Free Survival (PFS) and Overall Survival (OS)

- At the cut-off (October 21, 2020), all 29 subjects had completed at least their first assessment, 21 (72.4%) had been assessed with disease progression.
- Fourteen (14/29) (48.3%) subjects had died.

Table 2 Snapshot Median Progression Free Survival (PFS) and Survival (censored at last known no disease progression or last known alive) from diagnosis (Grade IV); data cut-off October 21, 2020

	Reference Data[9,10]	Starting Dose of VAL-083			
		Overall (N=29)	**20 mg/m^2/d (N=1)**	**30 mg/m^2/d (N=25)**	**40 mg/m^2/d (N=3)**
Median PFS (months) (95%CI)	5.3[9] (5.0-7.6)	9.3 (6.4-12.0)	3.0 -	8.7 (6.4-12.5)	9.9 (9.3-9.9)
Number Progressed (%)	6.9[10] (5.0-12.5)	21 (72.4%)	1 (100%)	18 (72.0%)	2 (66.7%)
Median OS (months) (95%CI)	12.7[9] (11.6-14.4)	19.6 (12.0-22.4)	9.5 -	18.2 (12.0-20.9)	22.4* -
Number of deaths (%)	16.0[10] (9.1-28.7)	14 (48.3%)	1 (100%)	12 (48%)	1 (33.3%)

Tumor Response

- Best Response has been determined, as determined by the investigator, for subjects who completed their first planned assessment prior to cycle 4 (PreC4). Two subjects discontinued/died before first planned assessment time point (preC4).
- At the start of treatment (baseline), 5 patients receiving 30 mg/m^2/d had tumor below measurable level (BML) and continued to be assessed as BML at least through to the end of cycle 7, and were assessed by investigator as "CR"
- Patients with measurable tumor at baseline, tumor responses prior to cycle 4 were assessed as follows:

Table 3 Best response assessed prior to the start of cycle 4 in patients with measurable tumor at baseline

Best Response PreC4	PD	SD	CR	Discontinued/ Death	N
Overall	2 (8.3%)	13 (54.2%)	7 (29.2%)	2 (8.3%)	24
20 mg/m^2/day	1 (100%)	0 (0%)	0 (0%)	0 (0%)	1
30 mg/m^2/day	1 (5.0%)	12 (60.0%)	5* (25.0%)	2 (10.0%)	20
40 mg/m^2/day	0 (0%)	1 (33.3%)	2 (66.7%)	0 (0%)	3

*At 30 mg/m^2/day, including patients with BML tumor, a total of 10 patients (10/25; 40%) were assessed as CR

Treatment Cycles

Overall in the study, 18/29 (62.1%) patients completed 8 cycles or more of VAL-083 treatment and 14/29 (48.3%) patients completed 10 cycles or more of VAL-083 treatment. The median number of cycles completed by all patients and those with a starting dose of 30 mg/m^2/day was 9 (range 2-13) treatment cycles.

CONCLUSIONS and FUTURE DIRECTIONS

- VAL-083 at 30 mg/m^2/day in combination with radiation therapy is generally safe and well-tolerated, and multiple treatment cycles in the adjuvant setting have been achieved
- Adverse events have been consistent with prior studies
- Pharmacokinetics are predictable and levels of VAL-083 measured in the CSF at 2 hrs post-infusion were as high as those measured in plasma demonstrating significant penetration to the brain
- VAL-083 at 30 mg/m^2/day in combination with radiotherapy has demonstrated benefit with respect to disease progression and overall survival over standard-of-care (TMZ: 5.3 - 6.9 months and 12.7-16.0 months, respectively) in the same setting[9,10].
- VAL-083 will be evaluated further in GCAR's Glioblastoma Adaptive Global Innovative Learning Environment (GBM AGILE) Study. This trial is an adaptive clinical trial platform in glioblastoma multiforme (GBM): Newly diagnosed patients post-chemoradiation (radiation + TMZ); and patients with recurrent GBM. Patients with both methylated- and unmethylated–MGMT promoter will be enrolled.

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