Poster # CT172

Phase 2 clinical trial of dianhydrogalactitol (VAL-083) in patients with newly diagnosed MGMT-unmethylated GBM

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ABSTRACT #5210

Glioblastoma (GBM) is the most common and aggressive primary brain cancer. The majority of GBM patients have an unmethylated MGMT promoter status, leading to limited response to Temozolomide (TMZ) and decreased survival. Current standard-of-care includes surgery followed by chemoradiation and TMZ. An unmethylated promoter for O6-methylguanine DNA methyltransferase (MGMT) is a validated biomarker for TMZ-resistance and is strongly correlated with poor outcomes. VAL-083 is a novel bi-functional DNA targeting agent that induces inter-strand cross-links at N7-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 is being conducted 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/m2/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, dose-escalation, has identified a recommended dose of 30 mg/m2/day of VAL-083 in combination with RT as generally safe and well-tolerated. Stage 2, an expansion stage, has enrolled 20 additional patients at 30 mg/m2/day IV infusion on days 1, 2, and 3 of 21-day cycles. As of January 11, 2021, all 29 subjects in the study have been enrolled and completed the treatment stage of the study. Tumor response are 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. The trial is continuing as planned and an update on primary results on safety and efficacy, and pharmacokinetics will be provided 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 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.

REFERENCES

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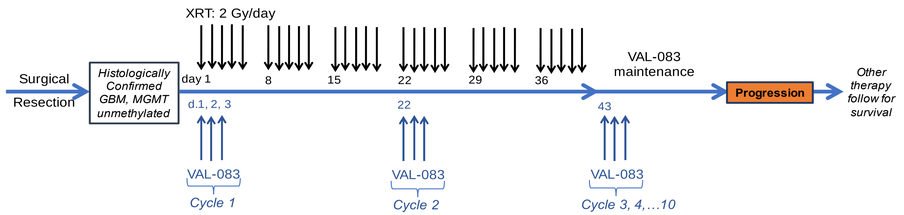
STUDY DESIGN

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 (MTD) 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

STUDY STATUS

As of the cut-off date of March 11, 2021:

- This study has been fully enrolled and all patients have completed treatment with VAL-083 and are currently in follow-up
- 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.
- 22/29 (75.9%) of subjects had disease progression
  - 2/29 (6.9%) subjects died before their first planned assessment at the end of cycle 3 due to disease progression.
  - 20/27 (74.1%) who completed at least end of cycle 3 assessments had been assessed with disease progression.
- 16/29 (55.2%) subjects had died

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%) Dose Limiting Toxicities (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

TREATMENT CYCLES COMPLETED

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. For those with a starting dose of 30 mg/m^2/day, the median number of treatment cycles completed was 9 (range 2-13).

PROGRESSION FREE SURVIVAL (PFS) AND OVERALL SURVIVAL (OS)

Data at the cut-off (March 11, 2021):

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 March 11, 2021

	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)	5.3[9]	9.3	3.0	8.7	9.9
(95%CI)	(5.0-7.6)	(6.4-12.0)	-	(6.4-12.5)	(9.3-9.9)
Number Progressed	6.9[10]	22	1	19	2
(%)	(5.0-12.5)	(75.9%)	(100%)	(76.0%)	(66.7%)
Median OS (months)	12.7[9]	19.6	9.5	19.1	28.0*
(95%CI)	(11.6-14.4)	(14.0-22.4)	-	(12.0-22.3)	-
Number of deaths	16.0[10]	16	1	14	1
(%)	(9.1-28.7)	(55.2%)	(100%)	(56.0%)	(33.3%)

* Actual survival time for 1 subject

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 start of cycle 4 in patients with measurable tumor at baseline.

Best Response Pre C4	N	PD	SD	CR	Discontinued/Death
Overall	24	2 (8.3%)	13 (54.2%)	7 (29.2%)	2 (8.3%)
20 mg/m^2/day	1	1 (100%)	0 (0%)	0 (0%)	0 (0%)
30 mg/m^2/day	20	1 (5.0%)	12 (60.0%)	5 (25.0%)*	2 (10.0%)
40 mg/m^2/day	3	0 (0%)	1 (33.3%)	2 (66.7%)	0 (0%)

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

CONCLUSION 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, with myelosuppression has been the most common adverse event
- 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 is being 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 are being enrolled.