Clinical Trial of VAL-083 in Newly Diagnosed MGMT-unmethylated GBM: Half-Way Report

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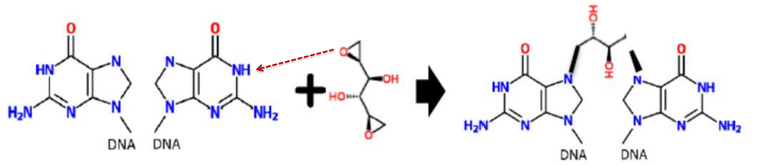
ABSTRACT #ACTR-06

Approximately 60% of glioblastoma multiforme (GBM) patients possess an unmethylated methylguanine DNA-methyltransferase (MGMT) gene, which confers a limited response to standard of care treatment with temozolomide (TMZ) resulting in a lower survival. VAL-083 is a novel bi-functional DNA targeting agent that induces interstrand cross-links at N^7-guanine, leading to DNA double-strand breaks and ultimately cell death. VAL-083 circumvents MGMT-mediated repair of the O^6 guanine alkylator TMZ. 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 and induction format to confirm the recommended dose of VAL-083 when administered concurrently with radiation therapy (RT) based on safety and tolerability. The subjects received VAL-083 at 20, 30, or 40 mg/m^2/day x 3 days every 21 days along with standard radiation treatment. Stage 2 comprises an expansion phase to enroll up to 30 patients. 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. As of 17th May, 2019, 18 patients have been enrolled. Fifteen patients have completed their prospectively planned MRI scans and had their initial assessment for tumor progression. Of these 15 patients, seven were assessed as a complete response (CR), and eight patients as having stable disease (SD). Of the remaining three patients, one died prior to their post-cycle 3 MRI and two have not been on study long enough to reach their planned post-cycle 3 MRI. As of the data cutoff, 14 of the 18 patients were still alive. Consistent with our prior experience, myelosuppression was the most common adverse event. Three dose-limiting toxicities have been reported - one at the 40 mg/m^2/day and two at the 30 mg/m^2/day dose. Further enrollment, safety & study updates will be presented at the meeting. Clinicaltrials.gov identifier: NCT03050736.

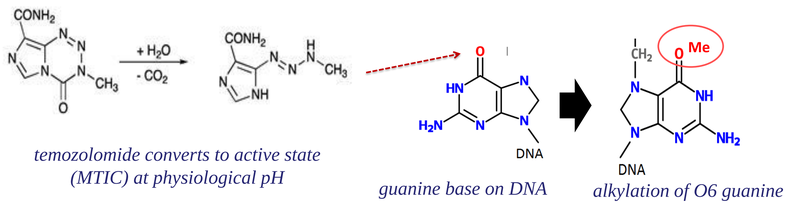
BACKGROUND

Mechanism of VAL-083 via crosslinks at N7 of guanine



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

Mechanism of temozolomide (TMZ) via alkylation at O6 of guanine



temozolomide converts to active state (MTIC) at physiological pH — *guanine base on DNA* — *alkylation of O6 guanine*

Figure 1. *The N7-targeting mechanism of action of VAL-083 differs from those of O6-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 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 radio-sensitizer 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).

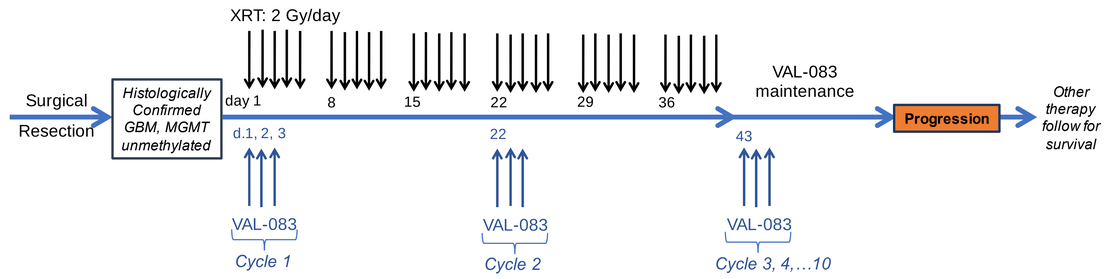
Table 1. **Historical data comparing randomized clinical trials of VAL-083 versus other chemotherapies used in the treatment of high-grade gliomas**

		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 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)[9]. 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

STUDY UPDATE

As of November 2nd, 2019:

- ❖ 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 have been 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
- ❖ A total of 23 subjects have been treated in the study
- ❖ 14 subjects have been treated in the Expansion Phase with a starting dose of 30 mg/m^2/day
- ❖ Overall, 7/23 (30.4%) of subjects have 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 4/23 (17.4%) of subjects
- Three DLTs have been reported in subjects who completed the first 2 cycles of treatment:

Table 2. Subjects with Dose-Limiting Toxicities (DLTs) during the first 42 days (2 cycles of treatment)

VAL-083 Dose (mg/m^2/day	Number of Subjects Completed 42 Days Treatment (2 cycles)	Number of Subjects with Dose Limiting Toxicities
20	1	0 (0%)
30	18	2 (11.1%)
40	3	1 (33.3%)

Pharmacokinetics

- Pharmacokinetic profiles are being 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 is as high in CSF as in plasma at 2 hours post-infusion

Table 3: Concentration of VAL-083 in Plasma and CSF

		Mean VAL-083 (SD) Conc. (ng/mL)			
Dose (mg/m^2/d)	**N**	**Plasma C_{max}**	**Plasma 2 hr post dose**	**CSF 2 hr post dose**	**Ratio @ 2 hr CSF/Plasma**
20	1	481.0	110.0	154	1.40
30	6	574.9 (261.5)	97.2 (20.9)	123.0 (27.8)	1.19 (0.37)
40	3	898.7 (69.6)	169.7 (41.9)	189.7 (69.9)	1.13 (0.41)

Progression Free Survival

As of the cut-off date of November 2nd, 2019:

- For all subjects (completed and active treatment), the median number of cycles of VAL-083 received was 8; 9 subjects have received ≥ 10 cycles
- For the 22 subjects who had completed at least their first assessment, 12 had been assessed with disease progression
- Median progression free survival (PFS) (censored at last date alive):
  - All subjects: 9.9 (CI 7.3 – 12.0) months; 12/22 (54.6%) progressed
  - 20 mg/m^2/day: 3.0 months; 1/1 (100%) progressed
  - 30 mg/m^2/day: 10.4 (CI 6.0-12.0) months; 9/18 (50.0%) progressed
  - 40 mg/m^2/day: 9.9 (CI 9.3 to 9.9) months; 2/3 (66.6%) progressed
  - TMZ historical comparator 6.9 months

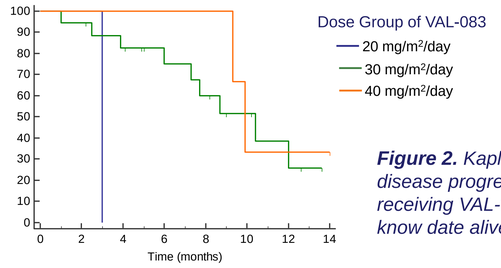


Figure 2. *Kaplan-Meier analysis of disease progression in subjects receiving VAL-083. Censored at last know date alive.*

Tumor Response

Best Response has been determined for subjects who completed their first planned assessment prior to cycle 4 (PreC4).

At November 2nd, 2019, 19 subjects had received at least one assessment prior to initiating C4 and beyond.

- 9/19 (47.4%) assessed as Complete Response
- 8/19 (42.1%) assessed as Stable Disease
- 2/19 (10.5%) assessed as Disease Progression

Two subjects not yet reached preC4 assessment; two subjects discontinued/died before first planned assessment time point (preC4).

CONCLUSIONS

- ➢ 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
- ➢ 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 over standard of care TMZ (6.9 months – Tanguturi et al, 2017)[9] in the same setting.

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