Phase 2 study of dianhydrogalactitol (VAL-083) in patients with MGMT-unmethylated, bevacizumab-naïve glioblastoma in the recurrent and adjuvant setting

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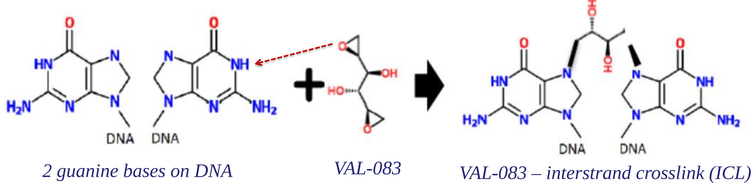
ABSTRACT #ACTR-12

Current standard-of-care for glioblastoma (GBM) includes surgery followed by concurrent therapy with radiation and temozolomide (TMZ) followed by adjuvant TMZ (days 1-5 every 28 days). Almost all GBM patients experience recurrent/progressive disease, with a median survival after recurrence of 3-9 months. Second-line treatment for recurrent GBM with bevacizumab (BEV) has not improved survival, and effective therapies for GBM are lacking. Unmethylated promoter for O^6-methylguanine-DNA-methyltransferase (MGMT) is a validated biomarker for TMZ-resistance and is correlated with poor patient prognosis. VAL-083 is a bi-functional DNA-targeting agent which rapidly induces interstrand DNA cross-links at N^7-guanine, induces double-strand breaks and acts independent of MGMT DNA repair. The current ongoing trial is a biomarker-driven Phase 2 study in MGMT-unmethylated BEV-naïve adult GBM. The primary objective of this study is to determine the effect of VAL-083 on median overall survival (mOS) for MGMT-unmethylated GBM patients compared to historical control. Secondary efficacy endpoints include progression-free survival (PFS), overall response rate (ORR), duration of response (DOR), and quality-of-life. Thirty-five (35) subjects with recurrent GBM have received 40 mg/m^2/day VAL-083 on days 1, 2, 3 of a 21-day cycle as the starting dose. Myelosuppression is the most common adverse event and a higher potential for this toxicity correlated with those patients who received a higher number of cycles of prior TMZ maintenance therapy, (>5 cycles vs. ≤5 cycles, p< 0.05). To minimize the potential for hematological toxicity in rGBM, subsequent subjects initiated treatment at 30 mg/m^2/d VAL-083 x 3 consecutive days every 21 days. In addition, since TMZ is of limited value in the MGMT-unmethylated setting, a second arm in newly diagnosed GBM has been included to explore whether substituting TMZ with VAL-083 offers clinical benefit and extends the time to recurrence. Enrollment, safety data and study updates will be presented at the meeting. Clinicaltrials.gov identifier: NCT02717962.

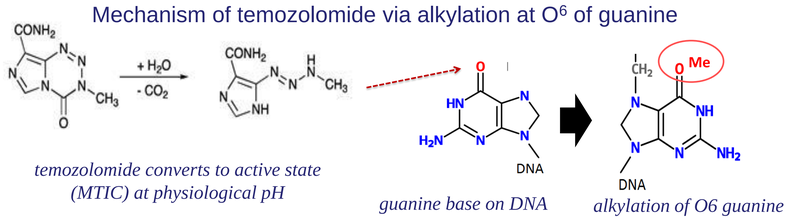
BACKGROUND

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 via alkylation at O^6 of guanine



temozolomide converts to active state (MTIC) at physiological pH *guanine base on DNA* *alkylation of O6 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 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 maintains cytotoxic activity in cancer cells deficient in DNA mismatch repair (MMR).[2,3] The N^7-targeting mechanism differs from temozolomide (TMZ) and nitrosoureas, enabling VAL-083 to overcome MGMT-mediated chemoresistance. This distinct mechanism of action of VAL-083 suggests that VAL-083 may offer a treatment alternative against tumors with MMR-, or MGMT-mediated resistance to chemotherapeutic agents, including temozolomide and nitrosoureas.[1,2,3]

STUDY UPDATE

As of November 15th, 2019:

- ❖ Recurrent Arm (Group 1) - total 83 subjects planned
  - 35 subjects enrolled with starting dose of 40 mg/m^2/day x 3 days every 21 days
  - 27 (of 48 planned) subjects enrolled with starting dose of 30 mg/m^2/day x 3 days every 21 days
- ❖ Adjuvant Arm (Group 2) - total 24 subjects planned
  - 5 subjects enrolled with a starting dose of 30 mg/m^2/day x 3 days every 21 days

The data presented provide assessments for the subjects who had completed at least 1 cycle of VAL-083 as of November 15th, 2019.

Lowering of starting dose from 40 to 30 mg/m^2/day

- A higher potential for myelosuppression with 40 mg/m^2/day VAL-083 in recurrent GBM subjects (Group 1) appeared to be correlated with the number of cycles of prior TMZ maintenance therapy, e.g. > 5 cycles
- Dose reduction was aimed at lowering the potential for myelosuppression and may increase the number of cycles of VAL-083 treatment a patient may receive and thus the potential efficacy of VAL-083 treatment

SAFETY

GROUP 1 (RECURRENT)

- ➢ Sixty (60) subjects have completed at least 1 cycle of treatment
- ➢ Similarly to prior experience with VAL-083, myelosuppression has been the most common adverse event observed
- ➢ Decreases in platelet and neutrophil counts generally resolved spontaneously
- ➢ 7/35 (20.0%) subjects experienced SAE possibly related to VAL-083 at a starting dose of 40 mg/m^2/day
- ➢ 4/25 (16.0%) subjects experienced SAE possibly related to VAL-083 at a starting dose of 30 mg/m^2/day
- ➢ Fewer subjects experienced a dose-limiting toxicity (DLT) at cycle 1 at 30 mg/m^2/day (Table 1)

Table 1. Dose-Limiting Toxicities during cycle 1 in Group 1 (Recurrent). All subjects completed at least 1 cycle. (Data cut-off November 15th, 2019)

Number and Percent of Subjects with DLT, as defined below	40 mg/m^2/d (n=35)	30 mg/m^2/d (n=25)	All (n=60)
Number of subjects with DLT*	8 (22.9%)	3 (12.0%)	11 (18.3%)
Grade 3 decreased platelet count with hemorrhage	0 (0%)	0 (0%)	0 (0%)
Grade 4 decreased platelet count	5 (14.3%)	1 (4.0%)	6 (10.0%)
Grade 3 decreased ANC (<500 µL) with fever (febrile neutropenia)	0 (0%)	0 (0%)	0 (0%)
Grade 3 decreased platelet count lasting more than 5 days	5 (14.3%)	2 (8.0%)	6 (10.0%)
Treatment delay >3 weeks (due to decrease platelet or ANC)	8 (22.9%)	2 (8.0%)	10 (16.6%)
Non-hematol. Grade 3/4 toxicity	1 (2.8%)	1 (4.0%)	2 (3.3%)
Dose reduction (Cycle 2)	9 (25.7%)#	2 (8.0%)##	11 (18.3%)

*Subjects may have experienced more than one DLT (listed above)
Dose reduction from 40 to 30 mg/m^2/day; ## Dose reduction from 30 to 20 mg/m^2/day

GROUP 2 (ADJUVANT)

- ➢ All 5 subjects have completed at least 1 cycle of treatment
- ➢ No SAEs, dose limiting toxicities or dose reductions (Cycle 2) have been recorded for this group

Tumor Response

- ❖ Tumor Assessment by MRI at the end of cycle 2 and every 42 days (every other cycle)
- ❖ Best Overall Response based on Investigator's clinical and radiologic assessment according to RANO criteria

GROUP 1 (RECURRENT)

Table 2. Best Tumor Response Measurement in Group 1 (Recurrent). All subjects completed at least 1 cycle. (Data cut-off November 15th, 2019)

Number of subjects completed first MRI assessment (Pre-Cycle3)	40 mg/m^2/d (n=35)	30 mg/m^2/d (n=23)	All (n=58)
Stable Disease	9 (25.7%)	6 (26.1%)	15 (25.9%)
No subjects demonstrated a partial response (PR) or complete response (CR)			

GROUP 2 (ADJUVANT)

First subject reached first MRI assessment at the end of cycle 2, with best overall response of stable disease (SD).

Overall Survival (Snapshot)

GROUP 1 (RECURRENT)

- ➢ Of the subjects who had completed at least 1 cycle of treatment, 31/35 subjects at 40 mg/m^2/day and 8/25 subjects at 30 mg/m^2/day had died.
- ➢ Median OS (mOS) snapshot (censored at last known date alive):
  - All subjects: 7.5 (CI 6.0-11.5) months
  - 40 mg/m^2/day dose: 6.5 (CI 4.4-9.0) months
  - 30 mg/m^2/day dose: 10.6 (CI 5.8 to 10.6) months; dose group enrollment and treatment ongoing

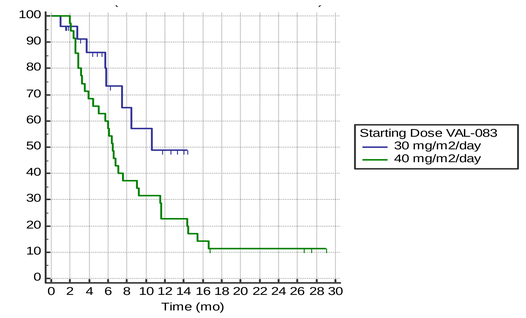


Figure 2. *Kaplan-Meier Survival Analysis of subjects receiving 30 or 40 mg/m^2/day VAL-083. Censored at last known date alive. Snapshot at data cut-off November 15th, 2019.*

GROUP 2 (ADJUVANT)

- ➢ As of November 15th 2019, all 5 subjects were continuing treatment.

CONCLUSIONS – FUTURE PLANS

- ➢ In the recurrent setting, 30 mg/m^2/day VAL-083 is better tolerated than 40 mg/m^2/day with fewer dose limiting toxicities
- ➢ To date VAL-083 is well tolerated as an alternative adjuvant treatment in unmethylated GBM to TMZ (which is of limited value in this setting[7]), and may offer a broader therapeutic window for VAL-083 and an opportunity to provide early intervention for these patients
- ➢ We continue to evaluate the efficacy of VAL-083 at the 30 mg/m^2/day dose which offers a potentially less toxic treatment in patients for treating recurrent disease

STUDY DESIGN

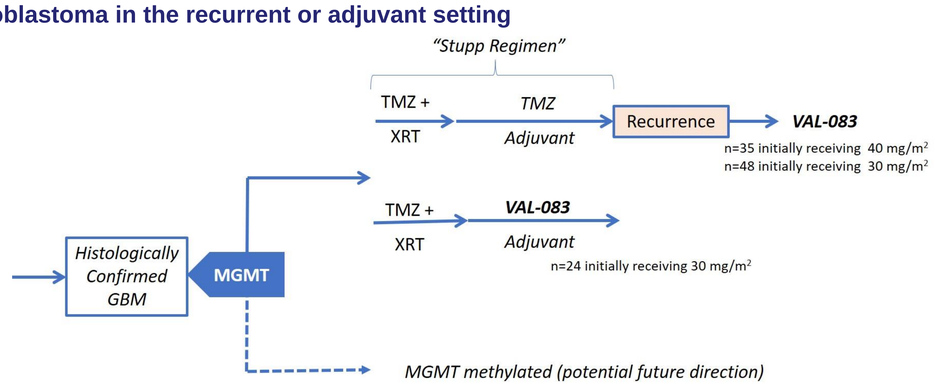
An open label, single-arm, biomarker-driven, Phase 2 study of VAL-083 treatment for MGMT unmethylated bevacizumab-naïve glioblastoma in the recurrent or adjuvant setting
(Clinicaltrials.gov Identifier: NCT02717962).

Group 1:

- To determine if treatment with VAL-083 improves overall survival (OS) in patients with *MGMT*-unmethylated recurrent GBM
- Comparison of survival will be made to historical control for lomustine of median OS = 7.2 months (EORTC 26101, for patients with recurrent *MGMT*-unmethylated GBM treated with lomustine alone)
- Up to 83 patients with recurrent/progressive GBM will be enrolled. This will include 35 patients initially treated at 40 mg/m^2/day and up to 48 patients initially treated at 30 mg/m^2/day

Group 2:

- To determine if treatment with VAL-083 in *MGMT*-unmethylated GBM improves progression-free survival (PFS) in newly diagnosed patients when given as adjuvant therapy post chemoradiation with TMZ
- Median PFS will be compared to historical control, temozolomide (6.9 months) (Tanguturi, et al. 2017)[8]
- Up to 24 newly diagnosed GBM patients who have completed chemoradiation treatment with TMZ and received no subsequent adjuvant TMZ will be enrolled



Link to trial on clinicaltrials.gov

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