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

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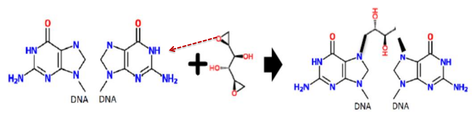
ABSTRACT #CT115

Glioblastoma (GBM) is the most common and aggressive primary brain cancer. Current standard-of-care includes surgery followed by concurrent therapy with radiation and temozolomide (TMZ) and maintenance TMZ. Almost all GBM patients experience recurrent/progressive disease, and median survival after recurrence is 3-9 months. Effective therapies for recurrent GBM (rGBM) are lacking, representing a significant unmet medical need. The unmethylated promoter for O^6-methylguanine-DNA-methyltransferase (MGMT) is a validated biomarker for TMZ-resistance and is correlated with poor prognoses. Second-line treatment with the anti-angiogenic agent bevacizumab (BEV) has not improved survival, and 5-year survival is less than 3%. VAL-083 is a bi-functional DNA-targeting agent that rapidly induces interstrand cross-links at N^7-guanine, leading to DNA double-strand breaks and cell-death. VAL-083's cytotoxicity is independent of MGMT status, and VAL-083 overcomes TMZ-resistance in GBM *in vitro* and *in vivo* models. We previously completed a 3+3 dose-escalation trial of VAL-083 in TMZ- and BEV-refractory rGBM. 40mg/m^2/day given on days 1-3 of a 21-day cycle was generally well-tolerated, and this dose was selected for further clinical evaluation in Phase 2 trials. The trial described here is an ongoing single-arm, biomarker-driven Phase 2 trial in *MGMT*-unmethylated BEV-naïve adult rGBM. In this trial, patients are receiving VAL-083 at 30 or 40mg/m^2/day on days 1-3 of a 21-day cycle. Tumor response is assessed by MRI approximately every 42 days, per RANO criteria. The primary objective of this study is to determine if VAL-083 improves median overall survival (mOS) for *MGMT*-unmethylated rGBM patients compared to a historical mOS of 7.1 months for such patients treated with lomustine (EORTC26101). Secondary efficacy endpoints include progression-free survival (PFS), overall response rate (ORR), duration of response (DOR), and quality-of-life (QOL) evaluation using the MD Anderson Symptom Inventory-Brain Tumor Module (MDASI-BT) self-reporting tool. Thirty-five (35) subjects have received 40 mg/m^2/day VAL-083 as the starting dose. Consistent with prior studies, myelosuppression (thrombocytopenia and neutropenia) is the most common adverse event in this study, and we observed that a higher potential for myelosuppression appears to be inversely correlated with the number of cycles of prior TMZ maintenance therapy, (>5 cycles *vs*. ≤5 cycles, p<0.05). Therefore, to minimize the potential for hematological toxicity in patients who have had significant prior TMZ maintenance therapy, subsequent patients in this study have initiated treatment with a starting VAL-083 dose of 30 mg/m^2/d x 3 every 21 days. Earlier initiation of maintenance treatment with VAL-083 in the therapeutic management plan, in lieu of maintenance TMZ in MGMT-unmethylated GBM patients is currently under consideration. Enrollment, safety data and protocol updates will be provided at the meeting. Clinicaltrials.gov identifier: NCT02717962.

BACKGROUND

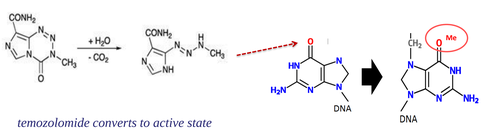
Mechanism of action of VAL-083 differs from that of temozolomide

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 via alkylation at O^6 of guanine

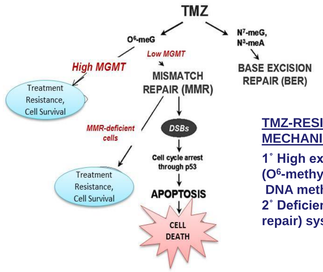


temozolomide converts to active state (MTIC) at physiological pH *guanine base on DNA* *alkylation of O6 guanine*

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 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 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.



TMZ-RESISTANCE MECHANISMS

1˚ High expression of MGMT (O^6-methylguanine DNA methyltransferase)
2˚ Deficient MMR (mismatch repair) system

FIGURE 2. *Diagram showing the primary (MGMT) and secondary (MMR) mechanisms of TMZ-resistance.*

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 *(cut-off date March 13th, 2019)*

- 47 of a total 48 initially planned subjects have been enrolled; 35 at a starting dose of 40 mg/m^2 and 12 at a starting dose of 30 mg/m^2;
- The data provide assessments for the 47 subjects who had completed at least 1 cycle of VAL-08 as of March 13th, 2019;
- 9/35 (25.7%) patients initially receiving 40 mg/m^2 exhibited stable disease (SD) per investigator assessment at the end of cycle 2;
- 4/10 (40.0%) patients initially receiving 30 mg/m^2 exhibited SD per investigator assessment at the end of cycle 2; two patients have not yet reached the end of cycle 2
- 7/35 (20.0%) patients initially receiving 40 mg/m^2 experienced a dose limiting toxicity at cycle 1;
- 1/12 (8.3%) patients initially receiving 30 mg/m^2 experienced a dose limiting toxicity at cycle 1;
- Similar to prior experience with VAL-083, myelosuppression has been the most common adverse event observed;
- 10 serious adverse events (SAEs), possibly related to treatment, have been observed in 8 study subjects to date, 6 at the 40 mg/m^2 dose, 2 at the 30 mg/m^2 dose;
- Decreases in platelet and neutrophil counts generally resolved spontaneously;
- Reductions in platelet and neutrophil counts appeared to be inversely correlated with the number of prior TMZ treatment cycles;
- Enrolment is currently ongoing with 3 subjects currently receiving treatment; 25 subjects have died; and 19 are being followed for survival;
- The initial study design is being expanded under protocol amendments;
  - Up to 35 additional patients will be enrolled at a starting dose of 30 mg/m^2 to enable analysis of the 30 mg/m^2 cohort at the originally planned statistical power;
  - An additional treatment group will be enrolled, comprising up to 24 newly diagnosed GBM patients who have completed chemoradiation treatment with TMZ and received no subsequent TMZ maintenance therapy, but will receive VAL-083 instead. This group will be included to explore whether earlier intervention with VAL-083 instead of TMZ maintenance therapy offers clinical benefit, and extends the time to recurrence as compared to TMZ maintenance therapy.

CONCLUSION AND FUTURE DIRECTIONS

- Myelosuppression (thrombocytopenia and neutropenia) is the most common adverse event with VAL-083. The higher potential for myelosuppression with 40 mg/m^2/day VAL-083 in this study appears to be correlated with the number of cycles of prior TMZ maintenance therapy, e.g. > 5 cycles;
- As a result, the starting dose of VAL-083 has been lowered from 40 to 30 mg/m^2 daily x 3 every 21 days, and the screening platelet count increased from 100,000/µL to 125,000/µL. These modifications may reduce the potential for myelosuppression and increase the number of cycles of VAL-083 treatment a patient may receive and thus the efficacy of VAL-083 treatment;
- VAL-083 at the 30 mg/m^2 dose offers a potentially less toxic treatment in patients who had received multiple maintenance cycles of TMZ for treating recurrent disease;
- The potential for VAL-083 as an alternative maintenance treatment in unmethylated GBM over TMZ (which is of limited value in this setting[7]), may offer a broader therapeutic window for VAL-083 and an opportunity to provide early intervention for these patients;
- Previous treatment with TMZ, particularly the number of prior cycles of maintenance therapy, may be useful as a guide for clinicians when determining optimal VAL-083 dosing;
- Earlier initiation of VAL-083 treatment in lieu of maintenance TMZ therapy in MGMT-unmethylated GBM patients will be studied through the additional treatment group added by protocol amendment.

STUDY DESIGN

Phase 2 study of VAL-083 treatment for MGMT unmethylated bevacizumab-naïve glioblastoma in the adjuvant or recurrent setting *(Clinicaltrials.gov Identifier: NCT02717962).*

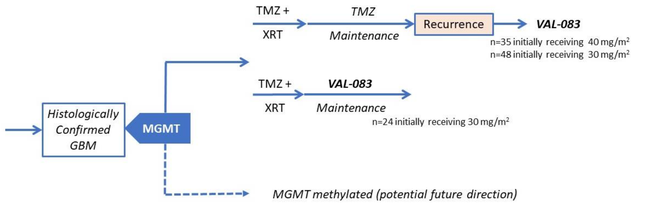
Link to trial on clinicaltrials.gov

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 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 and up to 48 patients initially treated at 30 mg/m^2;

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 maintenance therapy post chemoradiation with TMZ;
- Median PFS will be compared to historical control (Tanguturi SK, et al. 2017[8]);
- Up to 24 newly diagnosed GBM patients who have completed chemoradiation treatment with TMZ and received no subsequent maintenance TMZ will be enrolled.



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