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

Barbara J. O'Brien[1], John De Groot[1], Carlos Kamiya-Matsuoka[1], Shiao-Pei Weathers[1], Jeffrey A. Bacha[2], Dennis M. Brown[2], Anne Steino[2], John Langlands[2], Richard Schwartz[2], Sarath Kanekal[2], Lorena M. Lopez[2], and Marta Penas-Prado[3]

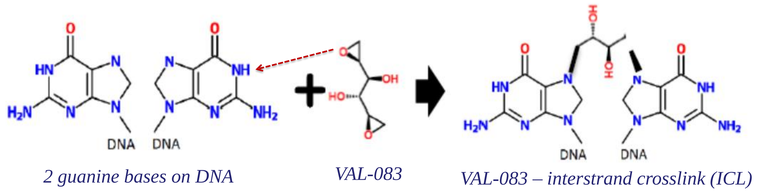
[1]Department of Neuro-Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]DelMar Pharmaceuticals, Inc., Vancouver, Canada and Menlo Park, California, USA; [3]Neuro-Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD

ABSTRACT #ACTR-27

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) followed by 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. Unmethylated promoter for O^6-methylguanine-DNA-methyltransferase (MGMT) is a validated biomarker for TMZ-resistance and is correlated with a poor prognosis. 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 rapidly inducing 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 cell lines, GBM cancer stem cells, and *in vivo* GBM models. We completed a 3+3 dose-escalation trial of VAL-083 in TMZ- and BEV-refractory rGBM. 40mg/m^2/day given on days 1,2,3 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, 48 patients will receive VAL-083 at 30 or 40 mg/m^2/day on days 1,2,3 of a 21-day cycle. Tumor response will be 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 7.15 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. Enrollment and safety data update will be provided at the meeting. Clinicaltrials.gov identifier: NCT02717962.

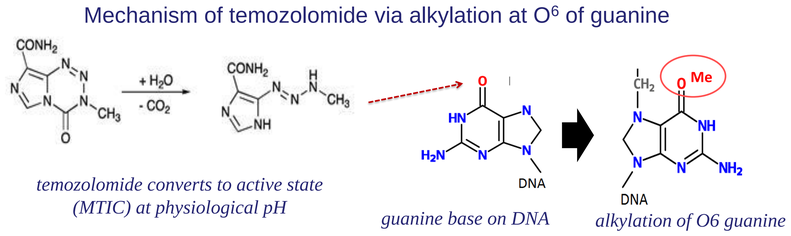
BACKGROUND

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

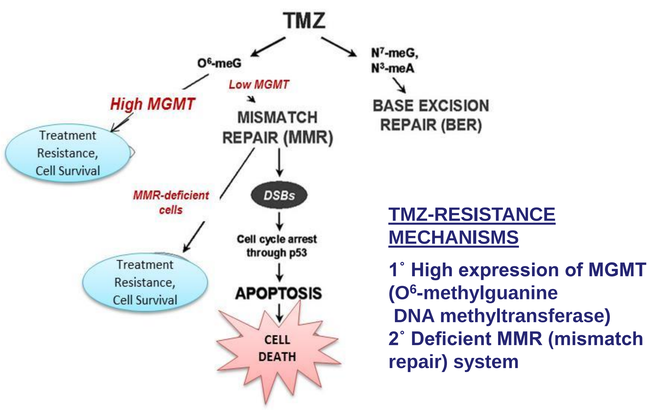


temozolomide converts to active state (MTIC) at physiological pH *guanine base on DNA* *alkylation of O6 guanine*

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 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

Table 1: Subject Demographics: 41 subjects (data cut-off Oct 15th, 2018)

Demographic	VAL-083 40 mg/m² (n=35)	VAL-083 30 mg/m² (n=6)	All (n=41)
Age: mean (range)	53.0 (31-72.5)	53.2 (39.2-67.6)	53.07 (31-72.5)
Sex: M/F	M: 19 (54.3%) F: 16 (45.7 %)	M: 3 (50%) F: 3 (50%)	M: 22 (53.7%) F: 9 (46.3%)
KPS: median (range)	80 (60-100)	90 (80-100)	80 (60-100)
BSA: mean (range)	2.00 (1.46-2.67)	1.96 (1.65-2.51)	2.00 (1.46-2.67)
Prior maintenance cycles with TMZ: median (range)	5 (1-12)	5 (3-12)	5 (1-12)
Weeks since last TMZ treatment: median (range)	6.1 (3.0-163)	8.25 (4.1-18.9)	6.3 (3.0-163)
Baseline platelet count (K/μL): mean (range)	212.5 (98.0-371.0)	176.7 (162.0-200.0)	207.2 (98.0-371.0)
Baseline ANC K/μL: mean (range)	5.07 (1.55-17.93)	5.29 (2.26-12.73)	5.10 (1.55-17.93)

All subjects are MGMT unmethylated, and all had prior TMZ treatment.

- 44 of total 48 subjects have been enrolled;
- The data presented provides assessments for the 41 subjects who had completed at least 1 cycle of treatment as of Oct 15th, 2018;
- 7 subjects are currently receiving treatment;
- 19 subjects have died, and 22 are being followed for survival;
- Study subjects received a median of 2 (range 1-12+) cycles of VAL-083; 12 subjects completed only 1 cycle of therapy;
  - Of those 12 subjects receiving 1 cycle only (all 40 mg/m^2), 2 discontinued treatment due to myelosuppression toxicity, 7 discontinued due to disease progression, 3 withdrew consent or were lost to follow-up.
- Of the 27 subjects that completed at least 2 cycles of treatment, 9/27 (33.33%) subjects exhibited stable disease (SD) at the end of cycle 2;
  - 8/23 (34.1%) initially receiving 40 mg/m^2 exhibited SD at the end of cycle 2;
  - 1/4 (25.0%) initially receiving 30 mg/m^2 exhibited SD at the end of cycle 2.

Table 3: Prior TMZ maintenance therapy cycles and subsequent myelosuppression for patients receiving 40 mg/m²/day VAL-083 (N=34#).

Prior TMZ maintenance cycles	≤5 (N=18)	>5 (N=16)
Prior TMZ maintenance cycles, median	4	8.5
Baseline platelet, K/μl: mean (range)	233 (149-371)	192 (98-320)
Dose Limiting Toxicity (hematological) - Cycle 1 of VAL-083	1 (5.5%)	6 (37.5%)*
VAL-083 dose reduction (hematol. - cycle 2) - actual or planned	3 (16.7%)	12 (75%)*
Thrombocytopenia (cycle 1)	3 (15%)	12 (86%)*
Median VAL-083 cycles	2.5	1.5

*#1 subject prior TMZ treatment unknown, and excluded from review. * P<0.05*

In the setting of prior maintenance treatment with TMZ, more myelosuppression has been observed in comparison to our phase 1/2 trial.[6] This suggests myelosuppression caused by prior TMZ maintenance therapy increases the risk for similar toxicity with VAL-083.

Table 2: Dose-Limiting Toxicities (DLTs) during cycle 1. All subjects completed at least 1 cycle. (Data cut-off date Oct 15th, 2018)

Number and Percent of Subjects with DLT, as defined below	40 mg/m² (n=35)	30 mg/m² (n=6)	All (n=41)
Number of subjects with DLT*	7 (20%)	1 (16.7%)	8 (19.5%)
Grade 3 decreased platelet count with hemorrhage	0 (0%)	0 (0%)	0 (0%)
Grade 4 decreased platelet count	5 (14.3%)	1 (16.7%)	6 (14.6%)
Grade 3 decreased ANC (<500 μL) with fever (febrile neutropenia)	0 (0%)	0 (0%)	0 (0%)
Grade 3 decreased platelet count (<50,000/μL) lasting more than 5 days.	1 (2.8%)	0 (0%)	1 (2.4%)
Treatment delay >3 weeks (due to decrease platelet or ANC)	6 (17.1%)	0 (0%)	6 (14.6%)
Non-hematol. grade 3/4 toxicity	1 (2.8%)	0 (0%)	1 (2.4%)
Dose reduction due to AE	7 (20%)	1 (16.7%)	8 (19.5%)

*Subjects may have experienced more than one DLT (listed above)

- Similar to prior experience with VAL-083, myelosuppression has been the most common adverse event observed;
- 10 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.

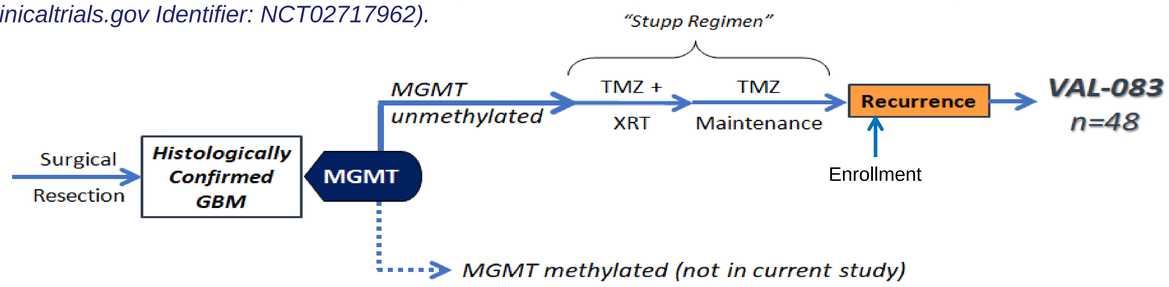
CONCLUSION AND FUTURE DIRECTIONS

- 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 inversely correlated with the number of cycles of prior TMZ maintenance therapy, e.g., > 5 cycles;
- As a result, in patients who have had prolonged prior TMZ maintenance therapy, 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 and 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 warrants further consideration.

STUDY DESIGN

An open label, single-arm, biomarker-driven, Phase 2 study of VAL-083 in patients with MGMT-unmethylated, bevacizumab-naïve recurrent GBM *(Clinicaltrials.gov Identifier: NCT02717962).*

Link to trial on clinicaltrials.gov



- Up to 48 patients with bevacizumab-naïve recurrent GBM with unmethylated-MGMT will be enrolled to determine if VAL-083 treatment will improves overall survival (OS) compared to historical reference control.
- Primary endpoint: Median OS will serve as the primary endpoint;
- Median OS in the MGMT-unmethylated lomustine arm of the EORTC26101 trial (7.15 months) will serve as the reference control.[5]
- Prior to Aug 2nd, 2018, 35 subjects received 40 mg/m^2/day on days 1,2, and 3 of every 21-day cycle as their starting dose. Subsequent subjects are receiving 30 mg/m^2/day on days 1,2, and 3 of every 21-day cycle as their starting dose.
- Secondary endpoints: Progression free survival (PFS), safety evaluations and symptom burden evaluation using MDASI-BT.

References:

1. **Zhai B, et al.** *Cell Death and Disease. (2018)9:1016.*
2. **Zhai B, et al.** *Cancer Res. July 2017: 77(13), abstract #2483.*
3. **Fouse S, et al.** *Neuro Oncol. (2014). v16(Supll 5), ET-18*
4. **Stupp et al.** *N Engl J Med 2005; 352(10):997-1003*
5. **Weathers et al.** *J Neurooncol;129(3): 487-94 (2016)*
6. **Shih K, et al.** *J Clin Onc, 34, 15_suppl. 2016, 2063-2063*
7. **NCCN guidelines** *(CNS cancers, 2017)*