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

Barbara J. O'Brien[1], Carlos Kamiya-Matsuoka1, Shiao-Pei Weathers[1], Alfred Yung[1], Monica Loghin[1], Rebecca Harrison[1], Nazanin Majd[1], Jeffrey A. Bacha[4], Dennis M. Brown[3], Anne Steino[3], Greg A. Johnson[3], Sarath Kanekal[3], John Langlands[3], Lorena M. Lopez[3], Richard Schwartz[3] and Marta Penas-Prado[2], John De Groot[1]

[1]Department of Neuro-Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Formerly affiliated with Department of Neuro-Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [3]DelMar Pharmaceuticals, Inc., Vancouver, Canada and Menlo Park, California, USA; [4]Formerly affiliated with DelMar Pharmaceuticals, Inc., Vancouver, Canada

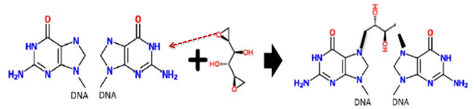
ABSTRACT # 10199 / POSTER # CT272

Glioblastoma (GBM) is the most common and aggressive primary brain cancer. 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 of 3-9 months after recurrence. Second-line treatment for recurrent GBM with bevacizumab (BEV) has not improved survival, and effective therapies for GBM are lacking. Unmethylated promoter status for O^6-methylguanine DNA methyltransferase (MGMT) is a validated biomarker for TMZ-resistance and is correlated with poor prognosis. VAL-083 is a bi-functional DNA-targeting agent rapidly inducing inter-strand 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. The trial described here is an open-label two-arm biomarker-driven phase 2 clinical trial in MGMT-unmethylated GBM patients with either recurrent (first recurrence) GBM (Group 1) or newly diagnosed GBM patients in the adjuvant setting after chemo-radiation with temozolomide (Group 2). Patients receive VAL-083 IV at 30 or 40 mg/m^2/day on days 1, 2, and 3 of a 21-day cycle. The primary objective of this study is to determine the effect of VAL-083 on median overall survival (mOS) in MGMT-unmethylated recurrent GBM patients (Group 1) compared to historical control, and progression-free survival (PFS) in newly diagnosed GBM patients requiring adjuvant therapy after chemo-irradiation with temozolomide (Group 2), compared to historical control. Secondary efficacy endpoints include PFS (Group 1), overall response rate (ORR), duration of response (DOR), and quality-of-life (QoL). Tumor response will be assessed by MRI approximately every 42 days, as per RANO criteria. The initial starting dose in this study was 40 mg/m^2/day, which was subsequently reduced to 30 mg/m^2/day to improve tolerance due to myelosuppression. As of 21st January 2020, thirty-five (35) subjects had enrolled at a starting dose of 40 mg/m^2/day, and 31 subjects had enrolled at a starting dose of 30 mg/m^2/day in Group 1, and 9 subjects enrolled at a starting dose of 30 mg/m^2/day in Group 2. As anticipated from prior studies with VAL-083, myelosuppression (thrombocytopenia and neutropenia) has been the most common adverse event observed. Clinicaltrials.gov identifier: NCT02717962

BACKGROUND

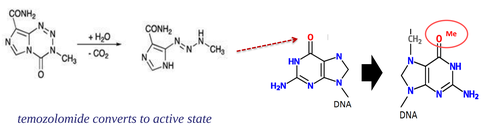
Mechanism of action of VAL-083 differs from that of temozolomide

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

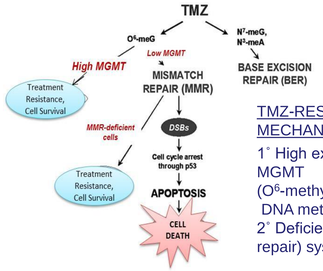


temozolomide converts to active state (MTIC) at physiological pH *guanine base on DNA* *alkylation of O6 guanine*

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]

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STUDY UPDATE *(cut-off date May 28, 2020)*

Group 1 (Recurrent)

- Seventy-two (72) subjects have completed at least one 21-day cycle of treatment:
  - 35 subjects have received a starting dose of 40 mg/m^2 VAL-083 I.V. x 3 days every 21 days.
  - To minimize the potential for hematological toxicity at 40 mg/m^2/day, subsequent subjects enrolled and initiated treatment at 30 mg/m^2/day VAL-083 I.V. x 3 days every 21 days.
  - 37 subjects have received a starting dose of 30 mg/m^2 VAL-083 I.V. x 3 days every 21 days; enrollment is continuing.
- Fewer subjects experienced a dose-limiting toxicity (DLT) at cycle 1 at 30 mg/m^2/day.

Table 1. Dose-Limiting Toxicities (DLT) during cycle 1 in Group 1 (Recurrent). All subjects completed at least 1 cycle. (Data cut-off May 28, 2020)

Number and Percent of Subjects with DLT, as defined below	40 mg/m^2/d (n=35)	30 mg/m^2/d (n=37)	All (n=72)
Number of subjects with DLT*	8 (22.9%)	3 (8.1%)	11 (15.3%)
DLT due to Hematological toxicity	8 (22.9%)	2 (5.4%)	10 (13.8%)
DLT due to Non-hematological Grade 3/4 toxicity	1 (2.8%)	1 (2.7%)	2 (2.7%)
Dose reduction (Cycle 2)	9 (25.7%)#	2 (5.4%)##	11 (15.3%)

*Subjects may have experienced more than one DLT (listed above);
Dose Limiting Toxicity (DLT) due to hematological toxicity included Gr 3 platelet count with hemorrhage, Gr 4 platelet count; Gr 3 ANC with fever, Gr 3 platelet count for >5 days; Treatment delay >3 weeks due to decreased platelet or absolute neutrophil count
Dose reduction from 40 to 30 mg/m^2/day I.V. x 3 consecutive days every 21 days; ## Dose reduction from 30 to 20 mg/m^2/day I.V. x 3 consecutive days every 21 days

- Of the subjects who had completed at least 1 cycle of treatment at 40 mg/m^2/day, 31/35 (88.6%) had died.
- Of the subjects who had completed at least 1 cycle of treatment at 30 mg/m^2/day, 20/37 (54.1%) had died; enrollment and treatment is ongoing at this starting dose level.
- Median OS (mOS) snapshot (censored at last known date alive) – cut-off date May 28,2020:
  - All subjects: 7.1 (CI 5.8-9.9) months
  - 40 mg/m^2/day dose: 6.5 (CI 4.4-9.0) months
  - 30 mg/m^2/day dose: 8.5 (CI 5.7 to 14.3) months; dose group enrollment and treatment is ongoing
- In Group 1, 6/35 (17.1%) subjects experienced SAE possibly related to VAL-083 at a starting dose of 40 mg/m^2/day; 4/37 (10.8%) subjects experienced SAE possibly related to VAL-083 at a starting dose of 30 mg/m^2/day.

Group 2 (Adjuvant)

- Nineteen (19) evaluable subjects have completed at least one 21-day cycle of treatment (total twenty-five (25) subjects enrolled); enrollment is continuing.
- Five (5/19; 26.3%) of subjects had exhibited disease progression; fourteen (14/19; 70%) subjects were continuing treatment; one (1) subject had discontinued treatment and was in follow-up
- As off the cut-off (May 28,2020), all 25 subjects enrolled in the study were alive at the cut-off date
- One (1/25; 4.0%) subject experienced a dose limiting toxicity during cycle 1
- In Group 2, 1/25 (4.0%) subjects experienced SAE possibly related to VAL-083 at a starting dose of 30 mg/m^2/day

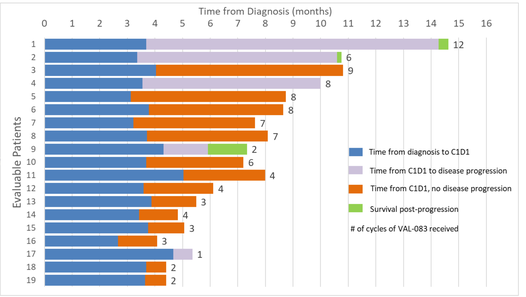

Figure 3. *Snapshot status of evaluable subjects (Group 2 Adjuvant) who have completed at least 1 cycle of treatment (data cut-off May 28, 2020).*

CONCLUSION AND FUTURE DIRECTIONS

- Similar to prior experience with VAL-083, myelosuppression has been the most common adverse event observed. Decreases in platelet and neutrophil counts generally resolved spontaneously.
- 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 adjuvant treatment in unmethylated MGMT GBM.
- VAL-083 in the adjuvant setting may offer an alternative therapy to TMZ for patients with MGMT unmethylated GBM (which is of limited value in this setting[7]), and an opportunity to provide early intervention for these patients.

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 linicaltrials.gov

Group 1:

- To determine if treatment with VAL-083 improves 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/d I.V. on 3 consecutive days every 21 days and up to 48 patients initially treated at 30 mg/m^2 /d I.V. on 3 consecutive days every 21 days;

Group 2:

- To determine if treatment with VAL-083 in *MGMT*-unmethylated GBM improves 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.