POSTER # CT238

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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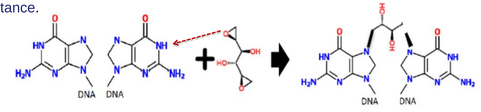
ABSTRACT # 5165 POSTER # CT238

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 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. The trial described here is an open-label two-arm biomarker-driven phase 2 clinical trial in MGMT-unmethylated GBM patients with either recurrent disease (Group 1) or newly diagnosed GBM patients requiring adjuvant therapy after chemoradiation with TMZ (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. For Group 1, 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 compared to historical control. For Group 2, the primary objective of this study is to determine the effect of VAL-083 on progression-free survival (PFS) in newly diagnosed GBM patients requiring adjuvant therapy after chemoradiation with TMZ, compared to historical control. Secondary efficacy endpoints include progression-free survival (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 January 11, 2021, 35 evaluable subjects have enrolled at a starting dose of 40 mg/m^2/day, and 46 evaluable subjects have enrolled at a starting dose of 30 mg/m^2/day in Group 1. In Group 2, 31 evaluable subjects had enrolled at a starting dose of 30 mg/m^2/day. As anticipated from prior studies with VAL-083, myelosuppression (thrombocytopenia and neutropenia) has been the most common adverse event observed. The trial is continuing as planned, and an enrollment, efficacy and safety data update will be provided at the meeting. Clinicaltrials.gov identifier: NCT02717962

BACKGROUND

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.



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

FIGURE 1. *The N^7-targeting mechanism of action of VAL-083*

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]

Group 1 (Recurrent GBM)

Safety (Snapshot at March 12, 2021)

- The main treatment related adverse events (Grade 3 and higher) have been decreased platelet counts, lymphocyte count, neutrophil count and headache.
- Fewer subjects experienced a Dose Limiting Toxicity (DLT) at cycle 1 at 30 mg/m^2/d than at 40 mg/m^2/d (Table 1).
- The frequency of patients experienced an SAE possibly related to VAL-083 at a starting dose of 30 mg/m^2 compared to those starting at 40 mg/m^2/d is as follows:
  - 5/35 (14.3%) subjects experienced an SAE possibly related to VAL-083 at a starting dose of 40 mg/m^2/day;
  - 7/54 (12.9%) subjects experienced an SAE possibly related to VAL-083 at a starting dose of 30 mg/m^2/day.
- The average number of cycles completed by patients at a starting dose of 40 mg/m^2 was 2.8, and at a starting dose of 30 mg/m^2 was 3.2

Table 1. Dose-Limiting Toxicities (DLT) during cycle 1 in Group 1 (Recurrent). All subjects completed at least 1 cycle. (Data cut-off March 12, 2021)

Number and Percent of Subjects with DLT, as defined below	40 mg/m^2/d (n=35)	30 mg/m^2/d (n=54)	All (n=89)
Number of subjects with DLT*	8 (22.9%)	3 (5.5%)	11 (12.4%)
DLT due to Hematological toxicity	8 (22.9%)	2 (3.7%)	10 (11.2%)
DLT due to Non-hematological Grade 3/4 toxicity	1 (2.8%)	1 (1.9%)	2 (2.3%)
Dose reduction (Cycle 2)	9 (25.7%)#	5 (9.3%)##	14 (15.7%)

*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

Overall Survival (OS) (Snapshot at March 12, 2021)

- Of the evaluable subjects (83/89; 93.3%) who had completed at least 1 cycle of treatment, 32/35 (91.4%) subjects at 40 mg/m^2/day and 37/48 (77.1%) subjects at 30 mg/m^2/day had died.
- Median OS (mOS) (Group 1-Recurrent) snapshot (censored at last known date alive) (Kaplan-Meier, MedCalc. v.19.7.2):
  - All subjects: 7.5 (CI 6.0-9.0) months
  - 40 mg/m^2/day dose: 6.5 (CI 4.4-9.0) months; dose group enrollment is complete, and treatment is complete
  - 30 mg/m^2/day dose: 7.9 (CI 5.9-9.9) months; dose group enrollment is complete, and treatment is ongoing

Group 2 (Adjuvant)

Safety (Snapshot at March 12, 2021)

- Three (3/36; 8.3%) subject experienced a Dose Limiting Toxicity (DLT) during cycle 1
- Six (6/36; 16.6%) subjects had a dose reduction from 30 to 20 mg/m^2/day at the start of cycle 2
- One (1/36; 2.8%) subject experienced SAE possibly related to VAL-083
- The average number of treatment cycles received by patients was 6.2 (range 1-13); n=33 evaluable subjects

Progression Free Survival (PFS) and Overall Survival (OS) (Snapshot at March 12, 2021)

- Twenty-four (24/33; 72.7%) of the evaluable subjects had exhibited disease progression; nine (9/33; 27.3%) subjects were continuing treatment
- Median PFS from diagnosis censored at last date no disease progression - 10.0 months (95%CI: 8.2-10.8) (Kaplan-Meier, MedCalc. v.19.7.2)
- As off the cut-off, eleven (11/33; 33.3%) evaluable subjects enrolled in the study had died.
- Median OS from diagnosis censored at date alive - 16.5 months (95%CI: 11.4-16.5) (Kaplan-Meier, MedCalc. v.19.7.2)

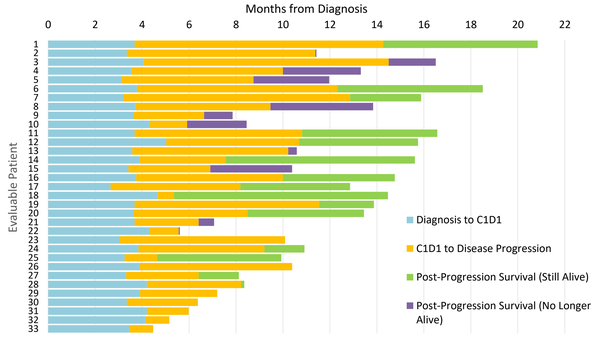


Figure 3. *Snapshot status of evaluable subjects (Group 2 Adjuvant) who have completed at least 1 cycle of treatment (data cut-off March 12, 2021).*

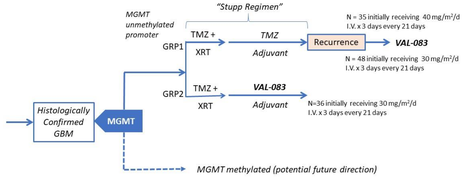
Phase 2 study of VAL-083 treatment for MGMT unmethylated bevacizumab-naïve glioblastoma in the adjuvant or recurrent setting

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)[5].
- Up to 83 evaluable patients with recurrent/progressive GBM will be enrolled. This will include 35 patients initially treated at 40 mg/m^2/d and up to 48 patients initially treated at 30 mg/m^2/d.

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)[6].
- Up to 36 newly diagnosed GBM patients who have completed chemoradiation treatment with TMZ and received no subsequent adjuvant TMZ will be enrolled.



(Clinicaltrials.gov Identifier: NCT02717962).

CONCLUSION AND FUTURE DIRECTIONS

- Consistent with prior studies, myelosuppression is the most common adverse event with VAL-083 in both recurrent GBM and in the adjuvant setting.
- We continue to evaluate VAL-083 at the 30 mg/m^2/day dose which appears to offer a potentially less toxic treatment than 40 mg/m^2/d, and potentially greater benefit in patients with recurrent disease compared to historical control[5].
- 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 provide an opportunity for early intervention and potential benefit for these patients compared to historical control[6].
- VAL-083 is being evaluated further in GCAR's Glioblastoma Adaptive Global Innovative Learning Environment (GBM AGILE) Study. This trial is an adaptive clinical trial platform in glioblastoma multiforme (GBM): Newly diagnosed patients post-chemoradiation (radiation + TMZ); and patients with recurrent GBM. Patients with both methylated- and unmethylated–MGMT promoter will be enrolled.

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 #248; 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: Wick, W et al (2017) N.Eng.J.Med. 377:1954-1963, 6: Tanguturi SK, et al. NeuroOncol;19(7):908-917 (2017); 7: NCCN guidelines (CNS cancers, 2017).