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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STUDY UPDATE

ABSTRACT #CTNI-72

Current standard-of-care for glioblastoma (GBM) includes surgery followed by concurrent therapy with radiation and temozolomide (TMZ) followed by adjuvant TMZ. Almost all GBM patients experience recurrent/progressive disease despite upfront standard-of-care treatment, with a median survival after recurrence of 3-9 months. 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 inter-strand cross-links at N^7-guanine inducing double-strand breaks causing cell death and acts independent of MGMT DNA repair. This trial is an open-label two-arm biomarker-driven phase 2 clinical trial in MGMT-unmethylated bevacizumab-naïve GBM patients with either recurrent (Group 1) or newly diagnosed GBM requiring adjuvant therapy after chemo-radiation with temozolomide (Group 2). Patients receive VAL-083 IV at 30 or 40 mg/m^2/d 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); and progression-free survival (PFS) in newly diagnosed GBM patients requiring adjuvant therapy after chemo-irradiation with temozolomide (Group 2), compared to historical controls in both groups. Tumor response will be assessed by MRI every 42 days, using RANO criteria. The initial starting dose in this study was 40 mg/m^2/d on days 1, 2, and 3 of a 21-day cycle, which was subsequently reduced to 30 mg/m^2/d to improve tolerance due to myelosuppression. As of June 2, 2020, 35 patients with recurrent GBM (Group 1) have received 40 mg/m^2/d and 39 patients have received 30 mg/m^2/d VAL-083. In the adjuvant setting (Group 2), 25 patients have been enrolled (30 mg/m^2/day). Enrollment, safety data and study updates will be presented at the meeting. Clinicaltrials.gov identifier: NCT02717962.

Background

VAL-083 is a novel bi-functional DNA targeting agent that rapidly induces inter-strand 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]

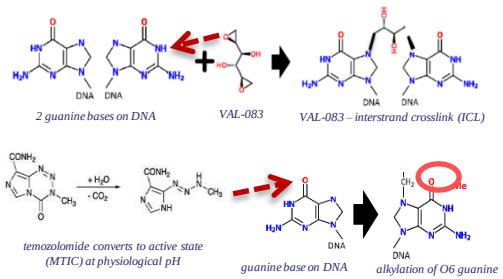


Figure 1. *The N^7-targeting mechanism of action of VAL-083 differs from those of O^6-alkylating agents like temozolomide and nitrosoureas.*

StudyStatus

As of October 23, 2020:

- Recurrent Arm (Group 1)
  - 35 subjects (34 efficacy evaluable) enrolled with starting dose of 40 mg/m^2/day x 3 days every 21 days - no further enrollment
  - 49 subjects (43 efficacy evaluable of 48 planned), enrolled with starting dose of 30 mg/m^2/day x 3 days every 21 days
- Adjuvant Arm (Group 2) - total 36 subjects planned
  - 30 subjects (27 evaluable of 36 planned), enrolled with a starting dose of 30 mg/m^2/day x 3 days every 21 days

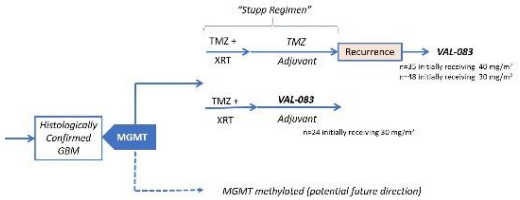
The data presented provide assessments for the subjects who had completed at least 1 cycle of VAL-083 as of October 23, 2020.

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

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)[5]
- 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)[7]
- Up to 36 newly diagnosed GBM patients who have completed chemoradiation treatment with TMZ and received no subsequent adjuvant TMZ will be enrolled

Group 1 (Recurrent GBM)

Safety

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 October 21, 2020)

Number and Percent of Subjects with DLT, as defined below	40 mg/m^2/d (n=35)	30 mg/m^2/d (n=49)	All (n=84)
Number of subjects with DLT*	8 (22.9%)	3 (6.1%)	11 (13.1%)
DLT due to Hematological toxicity	8 (22.9%)	2 (4.1%)	10 (11.9%)
DLT due to Non-hematological Grade 3/4 toxicity	1 (2.8%)	1 (2.0%)	2 (2.4%)
Dose reduction (Cycle 2)	9 (25.7%)#	5 (10.2%)##	12 (14.3%)

*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

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; 3/49 (6.1%) subjects experienced SAE possibly related to VAL-083 at a starting dose of 30 mg/m^2/day.

Pharmacokinetics

- Pharmacokinetic profiles determined on day 1 of cycle 1 indicate Cmax and AUC are broadly linear with respect to dose.
- At 30 mg/m^2: Cmax - 477.7 (±123.8) ng/mL; AUC - 494.1 (±166.9) ng.hr/mL; t1/2 - 0.80 (±0.18) hr (n=22)
- At 40 mg/m^2: Cmax - 680.3 (±211.5) ng/mL; AUC - 660.7.2 (±251.2) ng.hr/mL; t1/2 - 0.84 (±0.24) hr (n=33)

Overall Survival (Snapshot at October 23, 2020)

- Of the evaluable subjects who had completed at least 1 cycle of treatment, 31/34 (91.2%) subjects at 40 mg/m^2/day and 24/43 (55.8%) subjects at 30 mg/m^2/day had died.
- Median OS (mOS) snapshot (censored at last known date alive) (Kaplan-Meier, MedCalc. v.19.5.3):
  - All subjects: 7.6 (CI 6.4-10.6) months
  - 40 mg/m^2/day dose: 6.5 (CI 4.4-9.2) months
  - 30 mg/m^2/day dose: 8.5 (CI 6.8-13.7) months; dose group enrollment and treatment ongoing

Group 2 (Adjuvant)

Safety

- Two (2/30; 6.7%) subject experienced a dose limiting toxicity during cycle 1
- Three (3/30; 10%) subjects had a dose reduction from 30 to 20 mg/m^2/day at the start of cycle 2
- One (1/30; 4.0%) subject experienced SAE possibly related to VAL-083 at a starting dose of 30 mg/m^2/day

Pharmacokinetics

- Pharmacokinetic profiles determined on day 1 of cycle 1 with a starting dose of 30 mg/m^2
  - Cmax – 509.6 (±173.4) ng/mL; AUC – 580.8 (±358.3) ng.hr/mL; t1/2 - 0.86 (±0.17) hr (n=18)

Progression Free Survival And Overall Survival (Snapshot at October 23, 2020)

As of the cut-off date (October 23, 2020):

- The median number of treatment cycles received by patients was 8 (range 1-13); n=27 evaluable subjects
- Nineteen (19/27; 70.4%) of the evaluable subjects had exhibited disease progression; eight (8/27; 29.6%) subjects were continuing treatment
  - Median PFS from diagnosis (snapshot October 23, 2020) censored at last date no disease progression - 10.0 months (95%CI: 7.6-10.8) (Kaplan-Meier, MedCalc. v.19.5.3)
- As off the cut-off (October 23 ,2020), 5/27 (18.5%) evaluable subjects enrolled in the study had died.
  - Median OS from diagnosis (snapshot October 23, 2020) censored at last date no disease progression - 16.5 months (95%CI: ND) (Kaplan-Meier, MedCalc. v.19.5.3)

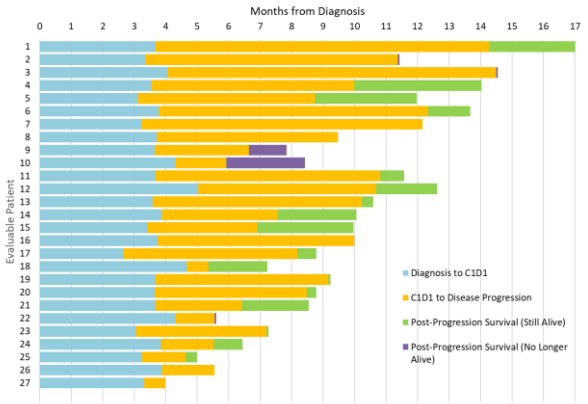


Figure 2. *Snapshot status of evaluable subjects (Group 2 Adjuvant) who have completed at least 1 cycle of treatment (data cut-off October 23, 2020).*

CONCLUSIONS – FUTURE PLANS

- Consistent with prior studies, myelosuppression is the most common adverse event with VAL-083 in both recurrent GBM and when used 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 and 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[6]), and may offer a broader therapeutic window for VAL-083 and an opportunity to provide early intervention and benefit for these patients
- VAL-083 will be 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 #2483; 3. Fouse S, et al. Neuro Oncol. (2014). v16(Suppl 5), ET-18; 4. Stupp R, 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. NCCN guidelines (CNS cancers, 2017); 7. Tanguturi SK, et al. NeuroOncol.19(7):908-917 (2017).