Poster # CTNI 21

# Phase 2 clinical trial of dianhydrogalactitol (VAL-083) in patients with newly diagnosed MGMT-unmethylated GBM

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## 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 differentiates it from other therapies used in the treatment of GBM, including TMZ.[2,3,4] VAL-083 is able to overcome TMZ-resistance in GBM, *in vitro* and *in vivo* and it acts as a radiosensitizer against GBM cancer stem cells *in vitro*.[3]

***Table 1:*** *Historical data comparing randomized clinical trials of VAL-083 versus other chemotherapies used in the treatment of high-grade gliomas. Reported median survival in combination with radiotherapy, and the benefit versus radiotherapy (XRT) alone is similar or superior to other DNA-targeting agents.*

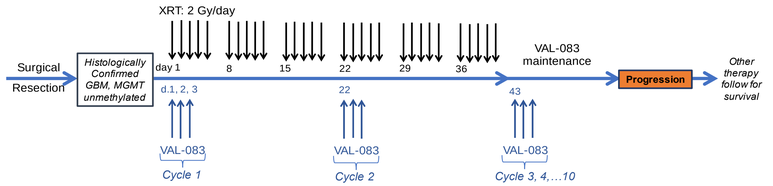
| | | | Nitrosourea therapy | |
|---|---|---|---|---|
| XRT + | VAL-083[5] | TMZ[6] | BCNU[7] | ACN[8] |
| Median survival (months) | 15.5 | 14.6 | 11.3 | 12.0 |
| *Benefit vs. XRT alone* | ***7.4*** | *2.5* | *2.8* | *n/a* |

This distinct mechanism of action of VAL-083 combined with results from historical clinical trials suggests that VAL-083 in combination with radiation therapy may offer a treatment alternative against GBM tumors with MGMT-mediated resistance to chemotherapeutic agents, including TMZ and nitrosoureas.

## STUDY DESIGN

An open label, single-arm, biomarker-driven, Phase 2 study of VAL-083 and radiation therapy in patients with newly diagnosed MGMT-unmethylated GBM.

*(Clinicaltrials.gov identifier NCT03050736).*




Newly diagnosed GBM with unmethylated-MGMT were treated with VAL-083 IV on days 1,2,3 of a 21-day cycle combined with radiotherapy (2Gy/day x 5 days) for 6 weeks followed by up to 8 cycles of VAL-083 maintenance therapy:

- Dose-escalation Phase : VAL-083 in cohorts (20, 30 and 40 mg/m$^2$/day IV) to assess safety and activity when administered concurrently with XRT to confirm the maximum tolerated dose (MTD).
- Expansion Phase: 20 additional patients at the determined maximum tolerated dose (MTD) of 30 mg/m$^2$/day VAL-083 administered concurrently with XRT. Primary endpoint was progression free survival (PFS) compared to historical references of TMZ at 5.3 months[9] and 6.9 months[10]. Tumor response were assessed by MRI, according to RANO criteria.
- Secondary endpoints included overall survival (OS), PK assessments of plasma and CSF, and safety and tolerability evaluations of VAL-083 in combination with a standard-of-care radiation regimen.

## 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: Golebiewska, et al. Acta Neuropathol. (2020) 140:919-949; 5: Eagan, et al. JAMA. (1979) 241(19):2046-5; 6: Stupp et al. N Engl J Med (2005) 352(10):997-1003; 7: Walker et al. N Eng J Med (1980), 303 (23), 1323-29; 8: Takakura K, et al. J Neurosurg. 64: 53-7 (1986); 9: Hegi et al N Eng J Med 352; 997-1003 (2005) 10: Tanguturi SK, et al. NeuroOncol. 19(7): 908-917 (2017)

## STUDY STATUS

- This study has been fully enrolled and all patients have completed treatment with VAL-083 and the follow-up period is complete.
- Dose escalation cohorts evaluated doses of 20, 30 and 40 mg/m$^2$/day on days 1, 2 and 3 of a 21-day cycle. As myelosuppression was observed at 40 mg/m$^2$/day, the dose of VAL 083 was reduced to 30 mg/m$^2$/day on days 1, 2 and 3 every 21 days, administered concurrently with radiation therapy for the dose expansion phase of the study.
- A total of 29 patients have been treated in the study: 1 patient received starting dose of 20 mg/m$^2$/day, 25 patients received a starting dose of 30 mg/m$^2$/day; 3 patients received a starting dose of 40 mg/m$^2$/day.

## SAFETY

***Table 2: Summary of Adverse Events, Serious Adverse events and Dose limiting Toxicities***

| Adverse Events | Serious Adverse Events | Dose Limiting Toxicities |
|---|---|---|
| Adverse event profile consistent with prior studies<br>• Most common adverse events: myelosuppression and anemia<br>• Hematological adverse events generally resolved spontaneously | SAEs possibly related to VAL-083 in 3/29 (10.3% subjects)<br>• Thrombocytopenia (2)<br>• Liver disorder (1) | DLTs in first 2 cycles of treatment in 3/29 (10.3%) of subjects<br>• One subject experienced a DLT at (1/3; 33%) at 40 mg/m$^2$/day<br>• Two subjects experienced a DLT at (2/25; 8%) at 30 mg/m$^2$/day<br>- 1 DLT was hematological<br>- 1 DLT non-hematological |

Overall in the study, 18/29 (62.1%) patients completed 8 cycles or more of VAL-083 treatment and 14/29 (48.3%) patients completed 10 cycles or more of VAL-083 treatment. For those with a starting dose of 30 mg/m$^2$/day, the median number of treatment cycles completed was 9 (range 2-13).

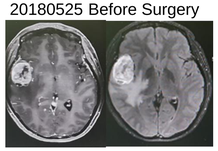
At 30 mg/m$^2$/day VAL-083, plasma Cmax was 746.2 ± 149.4 ng/mL. At 2 hrs post-infusion, the concentrations of VAL-083 in plasma and CSF were 107.8 ± 16 ng/mL and 127.1 ± 26.2 ng/mL, respectively, (ratio 1.24 ±00.35)

## CASE REPORT

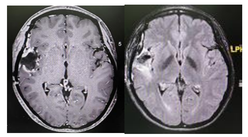
Female, 32 years. Resection right temporal lobe, MGMT unmethylated.
Chemoradiation: RT 60Gy/42 day, VAL-083 2 cycles (30 mg/m$^2$/day on days 1,2,3 of a 21-day cycle)
Adjuvant Treatment: VAL-083 – 11 cycles
- 30 mg/m$^2$/day on days 1-3 of a 21-day cycle for 9 cycles
- 20 mg/m$^2$/day on days 1-3 of a 21-day cycle for 2 cycles

Adverse Events: Grade 2 myelosuppression
Latest Tumor MRI (RANO): Complete Response (CR)
- PFS: >37 months
- OS: >37 months

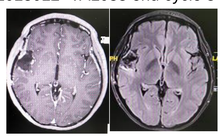
20180525 Before Surgery



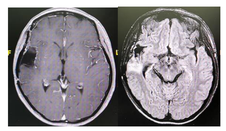
20180706 Before Val-083



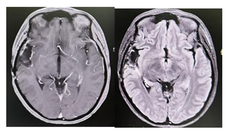
2018012 VAL083 end cycle 3



20190514 VAL083 end cycle 13



20210608 Last Follow-up



## PROGRESSION FREE SURVIVAL (PFS) AND OVERALL SURVIVAL (OS)

***Table 3: Median Progression Free Survival (PFS) and Overall Survival (OS) (censored at last known no disease progression or last known alive) from diagnosis (Grade IV)***

| | Reference Data[9, 10] | Starting Dose of VAL-083 | | | |
|---|---|---|---|---|---|
| | | Overall (N=29) | 20 mg/m$^2$/d (N=1) | 30 mg/m$^2$/d (N=25) | 40 mg/m$^2$/d (N=3) |
| Median PFS (months) (95%CI) | 5.3[9] (5.0-7.6) | 9.3 (6.4-12.0) | 3.0 - | 8.7 (6.4-12.5) | 9.9 (9.3-9.9) |
| Number Progressed (%) | 6.9[10] (5.0-12.5) | 22 (75.9%) | 1 (100%) | 19 (76.0%) | 2 (66.7%) |
| Median OS (months) (95%CI) | 12.7[9] (11.6-14.4) | 19.6 (14.0-22.4) | 9.5 - | 19.1 (12.0-22.3) | 32.3* - |
| Number of deaths (%) | 16.0[10] (9.1-28.7) | 18 (62.1%) | 1 (100%) | 15 (60%) | 2 (66.7%) |

### Tumor Response

- Best Response has been determined by the investigator, for subjects who completed their first planned assessment prior to cycle 4 (PreC4). Two subjects discontinued/died before first planned assessment time point (preC4).
- At the start of treatment (baseline), 5 patients receiving 30 mg/m$^2$/d had tumor below measurable level (BML) and continued to be assessed as BML at least through to the end of cycle 7, and were assessed by investigator as "CR"
- Patients with measurable tumor at baseline, tumor responses prior to cycle 4 were assessed as follows:

**Table 4 Best Response assessed prior to start of cycle 4 in patients with measurable tumor at baseline.**

| Best Response Pre C4 | N | PD | SD | CR | Discontinued/ Death |
|---|---|---|---|---|---|
| Overall | 24 | 2 (8.3%) | 13 (54.2%) | 7 (29.2%) | 2 (8.3%) |
| 20 mg/m$^2$/day | 1 | 1 (100%) | 0 (0%) | 0 (0%) | 0 (0%) |
| 30 mg/m$^2$/day | 20 | 1 (5.0%) | 12 (60.0%) | 5 (25.0%)* | 2 (10.0%) |
| 40 mg/m$^2$/day | 3 | 0 (0%) | 1 (33.3%) | 2 (66.7%) | 0 (0%) |

* At 30 mg/m$^2$/day, including patients with BML tumor, a total of 10 patients (10/25; 40%) were assessed as CR

## CONCLUSION AND FUTURE DIRECTIONS

- VAL-083 at 30 mg/m$^2$/day in combination with radiation therapy is generally safe and well-tolerated, and multiple treatment cycles in the adjuvant setting have been achieved.
- Adverse events have been consistent with prior studies, with myelosuppression has been the most common adverse event.
- Levels of VAL-083 in CSF were found to be at least as high as those in plasma.
- VAL-083 at 30 mg/m$^2$/day in combination with radiotherapy has demonstrated benefit over historical standard-of-care temozolomide (TMZ) in the same setting:
  - Disease progression: VAL-083 at 8.7 months *vs. temozolomide at 5.3[1] - 6.9[2] months.*
  - Overall survival: VAL-083 at 19.1 months *vs. temozolomide at 12.7[1] - 16.0[2] months.*
- VAL-083 is being evaluated further in GCAR's Glioblastoma Adaptive Global Innovative Learning Environment (GBM AGILE) Study (NCT03970447).