Phase 2 Study of VAL-083 and Radiotherapy in Newly Diagnosed MGMT-unmethylated GBM: Case Study Reports

Cheng-cheng Guo[1], Qun-ying Yang[1], Jia-wei Li[1], Shao-xiong Wu[1], Meilin Deng[1], Shaoyan Xi[1], Yixiang Liao[1], Jian-Gen Chen[1], Hai-rong Wang[1], Jeffrey Bacha[2], Sarath Kanekal[3], Claire Kwan[3], Gregory Johnson[3], Richard Schwartz[3], John Langlands[3], Dennis Brown[3], Zhong-ping Chen[1].

[1]Sun Yat-sen University Cancer Center, Guangzhou, China; [2]formerly affiliated with DelMar Pharmaceuticals, Inc., [3]Kintara Therapeutics, Inc., San Diego and Menlo Park, California, USA

Background

VAL-083 is a novel 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 radio-sensitizer 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.*

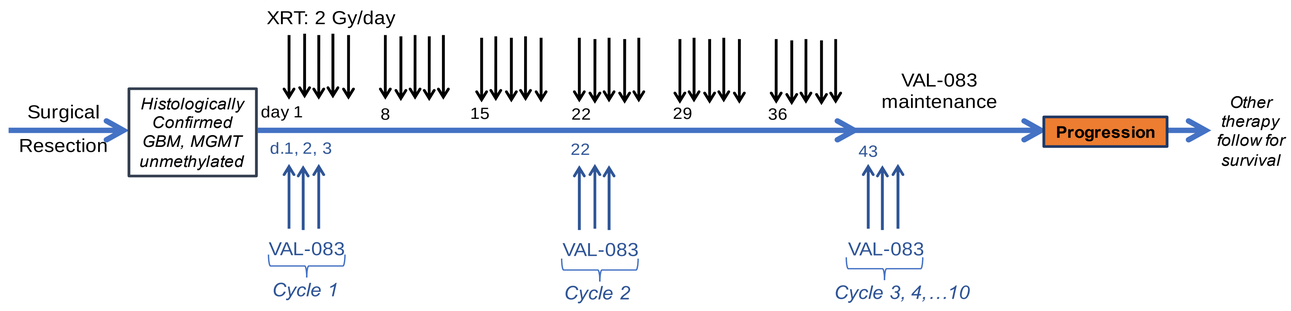
			Nitrosourea therapy	
XRT +	**VAL-083[4]**	**TMZ[5]**	**BCNU[6]**	**ACN[7]**
Median survival (months)	15.5	14.6	11.3	12.0
Benefit vs. XRT alone	***7.4***	*2.5*	*2.8*	*n/a*

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.

Here we report on two patient cases from this clinical study and follow-up treatment management and therapy, including outcomes after completion of the clinical study.

Clinical 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. Currently enrolling at Sun Yat-sen University Cancer Center *(Clinicaltrials.gov identifier NCT03050736).*



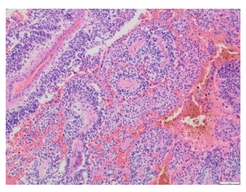
Newly diagnosed GBM with unmethylated-MGMT were treated with VAL-083 IV on days 1,2,3 of a 21-day cycle combined with radiotherapy (2Gy/day x 5 days) for 6 weeks followed by up to 8 cycles of VAL-083 maintenance therapy:

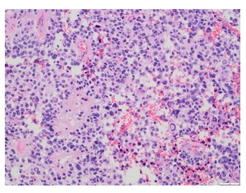
- A total of 29 patients were enrolled in the study and completed treatment, with 25 patients receiving 30 mg/m^2/day VAL-083.
- The median number of cycles completed by all patients was 9 (range 2-13).
- Consistent with our prior experience, myelosuppression was the most common adverse event.
- In a sub-group of patients, levels of VAL-083 in CSF were found to be at least as high as those in plasma.
- At study completion:
  - median progression free survival (PFS) for all patients enrolled was 9.3 (95%CI: 6.4-12.0) months
  - median overall survival for all patients enrolled was 19.6 (95%CI: 14.0-22.4) months.

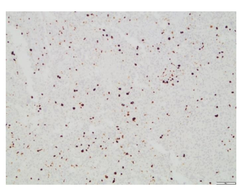
Case 1:

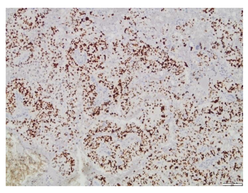
A 32-year-old woman presented with a 1-month history of headache was found to have a 40mm x 31mm x 41mm mass in the right temporal lobe.

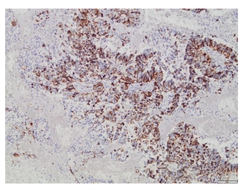
- Total resection of the tumor.
- Histopathology revealed hypercellular glial tissue with pseudopalisading necrosis and microvascular proliferation,
- Immunohistochemistry (IHC): positive staining for glial fibrillary acidic protein (GFAP) and Ki67 (+15%).
- The O6 -methylguanine-DNA methyltransferase (MGMT) promoter – unmethylated; Sanger sequencing revealed wild-type IDH1/2.
- The compilation of nuclear pleomorphism, nuclear atypia, microvascular proliferation, and necrosis were consistent with glioblastoma, WHO grade 4.

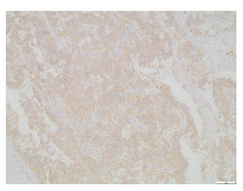

H&E x100


HE x200


KI67 X100

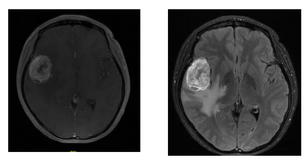

OLIG2 X100

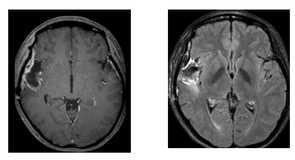

GFAP X100

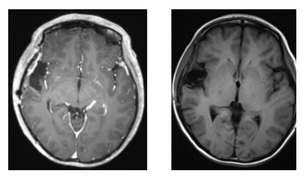

CAM X100

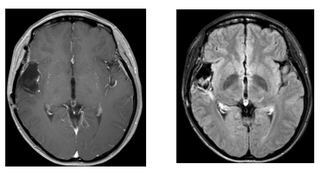
Therapy:

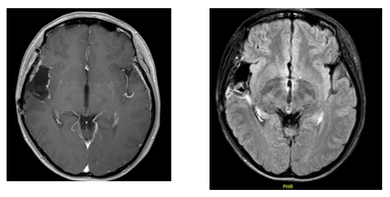
- Following surgery, the patient received conventional radiotherapy (60Gy) and chemotherapy with 13 cycles of VAL-083 (30mg/m^2/day for 10 cycles, 20mg/m^2/day for last 3 cycles.
- Routine MRI scans showed complete remission (last update 52.9 mo from start of treatment with VAL-083).

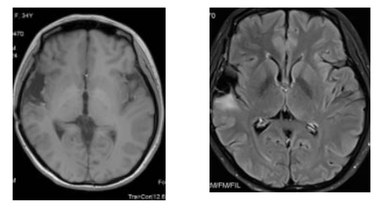

Pre-operation
The MRI revealed the enhanced lesion at the right temporal lobe

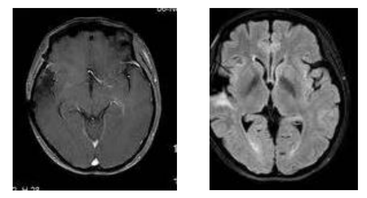

Post-resection of lesion in the right temporal lobe.
(MRI 4 days before C1D1 (Study day 1) of VAL-083)


MRI pre-Cycle 4 Day 1
(Study day 63)


MRI pre-Cycle 11 Day 1
(Study day 216)


After receiving 13 cycles of VAL-083
(Study day 308)


Treatment follow-up
(46 mo from surgery)


Treatment follow-up
(54 mo from surgery

- **Patient remained alive more than 4 years from diagnosis without relapsed disease.**

Case 2:

A 49-year-old man presented with a 2-month history of headache was found to have a 46 mm x 42 mm x 52 mm mass in the right frontal lobe.

- Total resection of the tumor was undertaken on 25th November, 2019.
- Histopathology: diffusely infiltrative neoplasm with astroglial, microvascular proliferation, and pseudo-palisading necrosis.
- Immunohistochemistry (IHC): positive staining for GFAP, MGMT and Ki67 (+30%), but negative staining for IDH1. Molecular testing shouwed MGMT promoter - unmethylated, IDH wild-type,
- Patient was diagnosed with GBM, WHO grade 4.

Therapy:

- Radiotherapy for a total dose of 60 Gy concurrent with VAL-083 for 2 cycles (30 mg/m^2/day cycle 1, 20 mg/m^2/day for cycle 2) during the radiation period.
- After completion of the 6-week radiotherapy regimen, adjuvant VAL-083 alone for another 10 cycles (20 mg/m^2/day).
- Routine MRI scans showed complete remission until April 2022 (29 mo after initial surgery).

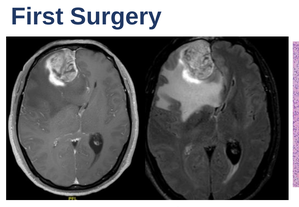
Recurrence:

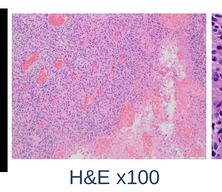
- A new nodule was found in the right frontal lobe in April, 2022 and was enlarged in June, 2022.
- The second surgery at other hospital was performed with complete resection of the lesion on 8th July, 2022.
- Histopathology showed mainly treatment-related changes: radiotherapeutic necrosis, brain tissue degeneration, hyalinized vessels, and meningeal thickening with inflammatory reaction, while tumor cells can be found locallywith irregular nuclei but seldom mitosis and lower Ki67 index, suggesting current diagnosis of Astrocytoma WHO Grade 2-3.

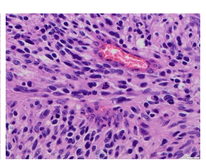
Therapy:

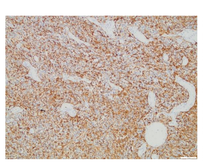
- VAL-083 as consolidation treatment on 8th October, 2022

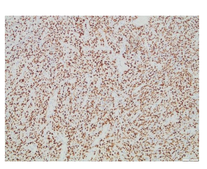
First Surgery

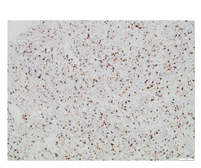

Pre-operation
Enhanced lesion R Frontal lobe

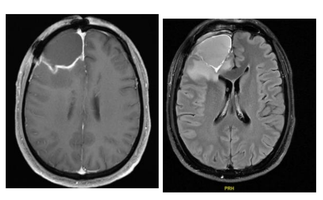

H&E x100

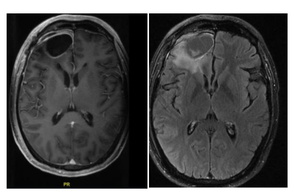

H&E x400

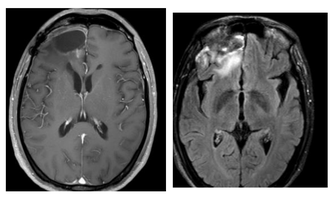

GFAP x100

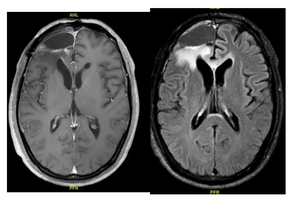

OLIG x100


KI-67 x100

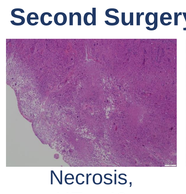

Study enrolment
(7 days pre- C1D1 (Study day 1)

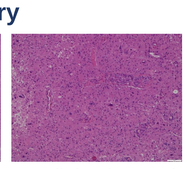

MRI pre-C3D1
(Study day 77)

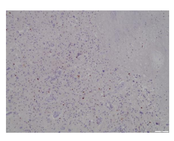

MRI pre-C8D1
(Study day 200)

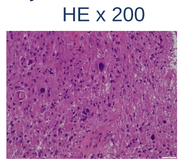

Post Tx Follow-up
(Study day 436)

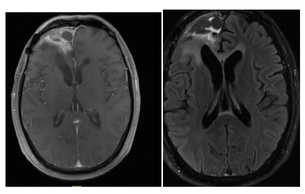
Second Surgery

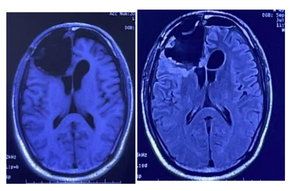

Necrosis,
HE x 40

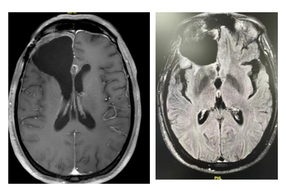

Hyalinized vessels,
HE x 200


Few Ki67,
X100


Abnormal cell degeneration HE x200


Considered recurrence pre-op)
(28.9 mo from C1D1 VAL-083)


Post-operation
(30.2 mo from C1D1 VAL-083)


Second Tx VAL-083
(32.9 mo from C1D1 VAL-083)

- **Patient remained alive up to last follow-up (Aug. 2023) for 45 months from initial diagnosis.**

Author Disclosure Information:
C. Guo: None. Q. Yang: None. J. Li: None. S. Wu: None. X. Cao: None. M. Deng: None. X. Du: None. J. Bacha: None. S. Kanekal: None. C. Kwan: None. G. Johnson: None. R. Schwartz: None. J. Langlands: None. D. Brown: None. Z. Chen: None.

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; 4. Eagan RT, et al. JAMA. 241(19): 2046-5 (1979); 5. Stupp R, et al. N Engl J Med. 352(10): 997-1003 (2005); 6. Walker MD, et al. Cancer Treat Rep. 60: 13-716 (1976); 8. Takakura K, et al. J Neurosurg. 64: 53-7 (1986).

Conclusion

The results from the study and these patient cases, support the potential benefit of VAL-083 as a treatment alternative against GBM tumors with MGMT-mediated resistance to TMZ.