Poster # CTNI 32

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

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BACKGROUND

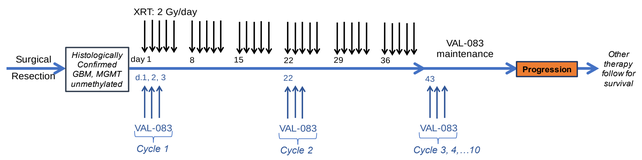
VAL-083 is a novel bi-functional DNA targeting agent that rapidly induces inter-strand cross-links at N^7-guanine, leading to DNA double-strand breaks (DSBs) and ultimately cell death.[1] VAL-083's unique cytotoxic mechanism circumvents O^6 -methylguanine-DNA methyltransferase (MGMT)-mediated chemoresistance 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]

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) administered concurrently with XRT to confirm the maximum tolerated dose (MTD).
- Expansion Phase: 20 additional patients at 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 Primary endpoint was progression free survival (PFS) compared to historical references of TMZ at 5.3 months[9] and 6.9 months[10].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

Safety and Pharmacokinetics

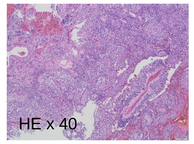
- Most common adverse events: myelosuppression and anemia; Hematological adverse events generally resolved spontaneously.
- SAEs possibly related to VAL-083 - 3/29 (10.3%): thrombocytopenia (2); liver disorder (1)
- Overall in the study, 18/29 (62.1%) patients completed 8 cycles or more of VAL-083 treatment and 14/29 (48.3%) patients completed 10 cycles or more of VAL-083 treatment. At 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)

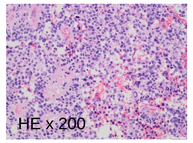
References

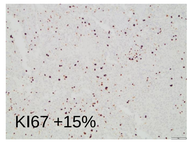
1: Zhai, B, et al. Cell Death and Disease. (2018) 9:1016; 2: Zhai, B, et al. Cancer Res. July 2017: 77(13), abstract #2483; 3: Fouse, S, et al. Neuro Oncol. (2014). v16(Suppl. 5), ET-18; 4: Golebiewska, et al. Acta Neuropathol. (2020) 140:919-949; 5: Eagan, et al. JAMA. (1979) 241(19):2046-5; 6: Stupp 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).

CASE REPORT 1

A 32-year-old woman who presented with a 1-month history of headache was found to have a 40mm*31mm*41mm mass in the right temporal lobe. After total removal of the tumor on 28th May 2018, histopathological examination revealed hypercellular glial tissue with pseudopalisading necrosis and microvascular proliferation. The compilation of nuclear pleomorphism, nuclear atypia, microvascular proliferation, necrosis, and Ki67 (+15%) are consistent with glioblastoma (WHO Gr 4). The MGMT promoter was confirmed to be unmethylated by methylation-specific polymerase chain reaction, and Sanger sequencing revealed wild-type IDH1/2. Following surgery, the patient received radiotherapy concurrent with VAL-083, and adjuvant maintenance therapy with VAL-083, for a total of 13 cycles (30 mg/m^2/day for 10 cycles, 20 mg/m^2/day for last 3 cycles) from 11th July, 2018 to 16th April, 2019. Routine MRI scans showed complete remission (last update Oct. 2022). She was alive more than 4 years from diagnosis without relapsed of disease.

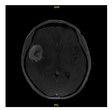


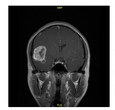




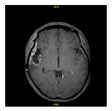
MGMT promoter was confirmed to be unmethylated by methylation-specific polymerase chain reaction

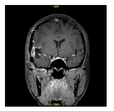
MRI of the patient from preoperative assessment, through cycle 13 of treatment with VAL-083 and follow-up 2 years and 10 months post treatment.



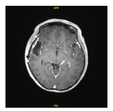


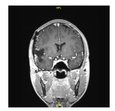
Pre-op 25 May 2018
The MRI revealed enhanced lesion at the right temporal lobe



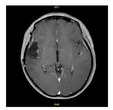


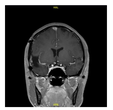
Enrolled 06 Jul 2018
Resection of lesion in right temporal lobe.



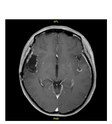


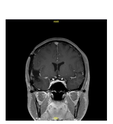
Pre-C4D1
11 Sept 2018



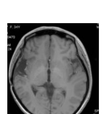


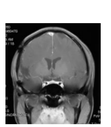
Pre-C11D1
11 Feb 2019





After 13 cycles of VAL-083
14 May 2019





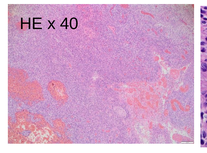
Follow-up
07 Mar 2022

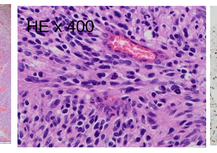
Table 1: Median Progression Free Survival (PFS) and Overall Survival (OS) (censored at last known no disease progression or last known alive) from diagnosis (Grade IV)

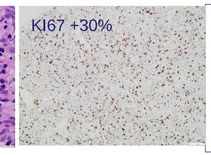
	Reference Data[9, 10]	Starting Dose of VAL-083			
		Overall (N=29)	20 mg/m^2/d (N=1)	30 mg/m^2/d (N=25)	40 mg/m^2/d (N=3)
Median PFS (months) (95%CI)	5.3[9] (5.0-7.6)	9.3 (6.4-12.0)	3.0 -	8.7 (6.4-12.5)	9.9 (9.3-9.9)
Number Progressed (%)	6.9[10] (5.0-12.5)	22 (75.9%)	1 (100%)	19 (76.0%)	2 (66.7%)
Median 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%)

CASE REPORT 2

A 49-year-old man who presented with a 2-month history of headache was found to have a 46mm*42mm*52mm mass in the right frontal lobe. After surgery (25th Nov, 2019), histopathological examination showed a diffusely infiltrative neoplasm with astroglia, microvascular proliferation, and pseudopalisading necrosis. IHC of the tumor demonstrated positive staining for MGMT and Ki67 (+30%), but negative staining for IDH1. Combined with molecular pathology of MGMT unmethylation, IDH wild-type, patient was diagnosed with GBM, WHO grade 4, and was enrolled this study. The patient received radiotherapy (60 Gy) concurrent with VAL-083 and adjuvant maintenance therapy with VAL-083 for a total of 12 cycles (30 mg/m^2/day for first cycle, 20 mg/m^2/day for following 11 cycles), 6th Jan 2020 to 24th Nov 2020. The patient was regularly followed-up with complete response until April 2022. A new nodule was found in the right frontal lobe in April, 2022 and was enlarged on June, 2022. A second surgery in another hospital was performed with complete resection of the lesion on 8th July, 2022. Histopathology showed mainly treatment-related changes: radiotherapeutic necrosis, brain degeneration, hyalinized vessels, and meningeal thickening with inflammatory reaction. Tumor cells can be found locally, with irregular nuclei but seldom mitosis and lower Ki67 index, suggesting current diagnosis of Astrocytoma, WHO Gr 2-3. The patient again received 2nd term chemotherapy of VAL-083 as consolidation treatment on 8th Oct, 2022 until Oct, 2022, he has remained alive for 2 years and 11 months since initial diagnosis.

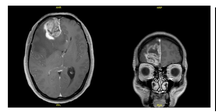




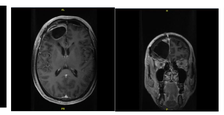


Pathology from 2nd surgery: showed mainly treatment-related changes: radiotherapeutic necrosis, brain degeneration, hyalinized vessels, and meningeal thickening with inflammatory reaction. Tumor cells can be found locally, with irregular nuclei but seldom mitosis and lower Ki67 index, suggesting current diagnosis of Astrocytoma, WHO Grade2-3.

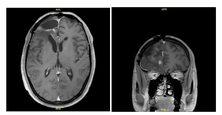
Patient MRI from preoperative assessment, through 12 cycles of VAL-083 and follow-up after 2nd surgery



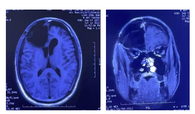
Pre-op 20 Nov 2022 The MRI revealed enhanced lesion at the right frontal lobe



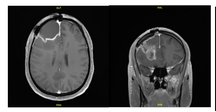
Pre-C3D1, 22 Mar 2020



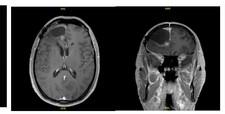
Follow-up, 16 Mar 2021



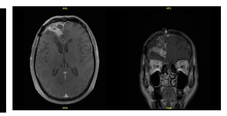
Following 2nd surgery 12 Jul 2022



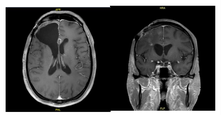
Enrolled 29 Dec 2019
Resection of lesion in right frontal lobe.



Pre-C8D1, 23 Jul 2020



Follow-up, suspect recurrence, 01 Jun 2022



Follow up,01 Oct 2022

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.
- 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.*
- The two case studies demonstrate the benefit of VAL-083 in newly diagnosed GBM when combined with radiotherapy and followed up as maintenance therapy