VAL-083 in patients with recurrent glioblastoma treated under expanded access program

Carlos Kamiya-Matsuoka[1], Shiao-Pei Weathers[1], Rebecca Harrison[2], Nazanin Majd[1], Ashley Aaroe[1], Stephanie Knight[1], Teresa Hanna[1], Chirag B. Patel[1], John Langlands[3], Dennis Brown[3], Vinay Puduvalli[1]

[1]Department of Neuro-Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]BC Cancer, The University of British Columbia, Vancouver, Canada; [3]Valent Technologies, LLC, Menlo Park, CA, USA.

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Background

Current standard-of-care for glioblastoma (GBM) includes surgery followed by chemoradiation with temozolomide (TMZ) followed by adjuvant TMZ. Almost all GBM patients experience disease progression despite upfront standard-of-care treatment, with a median overall survival of 3-9 months after first recurrence. There are limited treatment options available upon progression of disease. They often involve participation in clinical trials with promising new therapies, but patients may not meet the strictly defined entry criteria to participate in these clinical trials.

Here we report on 30 recurrent GBM patients we have treated with **VAL-083** under an Expanded Access (EA) Program. These patients were not eligible to participate in other clinical trials.

About VAL-083

- VAL-083 is a CNS penetrating[1,2] and DNA targeting agent that rapidly induces interstrand cross-links at O6- and N7-guanine, leading to DNA double-strand breaks (DSBs) and ultimately cell death.[3]
- VAL-083's unique cytotoxic mechanism circumvents MGMT-mediated chemoresistance and maintains cytotoxic activity in cancer cells deficient in DNA mismatch repair (MMR).[4,5]
- The N7-targeting mechanism differs from temozolomide (TMZ) and nitrosoureas. 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.[3, 4, 5]
- VAL-083 has been studied in phase 2 clinical studies for pMGMT-unmethylated recurrent GBM[6], as adjuvant therapy in newly diagnosed pMGMT-unmethylated GBM[6], and in combination with radiation therapy in newly diagnosed pMGMT-unmethylated GBM patients.[1,2]

Expanded Access Program and Patient Treatment

- Individual patients requested to access VAL-083 under an Expanded Access (EA) program (Clinicaltrials.gov Identifier: NCT03138629)
- Authorization and approval to proceed with treatment was received from the US Food and Drug Administration (USFDA) and MD Anderson Cancer Center Institutional Review Board.
- Patients treated under the EA program had recurrent GBM and initiated treatment between January 2020 and December 2023.
- EA patients received and initial starting dose of VAL-083 (30 mg/m^2) on day 1, 2 and 3 of a 21-day treatment cycle.
- Patient treatment approval and status, administration of VAL-083 and safety information was tracked using MedaSystems EA Management Platform.

Table 1: Treatment with VAL-083

Number of GBM patients treated under EA	30
Number of GBM patients with leptomeningeal disease (LMD)	4
Number of GBM patients treated under EA (evaluated for efficacy)	26

While safety data was assessed for all patients, those without LMD (26 patients) were evaluated for efficacy.

References

1: Guo, C, et al. Glioma, (2019) 2(4), 167-173; 2: Chen, Z-p, et al, Neuro-Oncol. (2021) 23(Suppl 6), vi63-vi64; 3: Zhai B, et al. Cell Death and Disease. (2018) 9:1016; 4: Zhai B, et al. Cancer Res. (2017): 77(13), abstract #248; 5: Fouse S, et al. Neuro Oncol. (2014). v16(Suppl 5), ET-18; 6: O'Brien, B et al. Neuro-Oncol. (2021) 23(Suppl 6), vi65-vi65

Patient Demographics

Table 2: EA Patient Demographics

Number of patients treated under EA (evaluated for efficacy)	26
Mean age yrs (range)	53.5 (22-67)
Sex (male)	19/26 (73.1%)
Median KPS (IQR)	80 (70-90)
Number of patients with >1 recurrence	12 (46.2%)
Number of patients with >2 recurrences	6 (23.1%)
Number of patients with multifocal disease	10 (38.5%)
Number patients with prior temozolomide Median number of prior cycles of temozolomide (range)	21 (80.8%) 7 (1-24)
Number patients with prior lomustine Median number of prior cycles of lomustine (range)	9 (34.6%) 1 (1-6)
Number of patients receiving concurrent bevacizumab	8 (30.8%)
Median time from last PD to start of VAL-083 (mo)	1.2 (95%CI: 0.52-2.4)
pMGMT–unmethylated	24 (92.3%)

The median number of mutations was 5 (range 0-10). Table 3 summarizes the most common mutations identified in these EA patients.

Table 3: Mutation Status of Patients Treated under EA (N=26)

IDH WT	25 (96.2%)	PIK3CA	3 (11.5%)
TERT	15 (57.7%)	ARTX	2 (7.7%)
PTEN	10 (38.5%)	CDK4	2 (7.7%)
TP53	7 (26.9%)	CDKN2B	2 (7.7%)
NF1	7 (26.9%)	FGFR3_TACC3_Fusion	2 (7.7%)
EGFR	6 (23.1%)	MDM2	2 (7.7%)
EGFRamp	5 (19.2%)	PIK3R1	2 (7.7%)
CDKN2A	3 (11.5%)	PTPN11	2 (7.7%)

The mean number of cycles of VAL-083 received by patients was 4.3 (±3.8), with a range of 1-18 cycles. Eleven patients (11/26; 42.3%) had 4 or more cycles of VAL-083.

Safety

All 30 patients treated under EA were evaluated for safety.

Myelosuppression was the primary adverse event

- 2/30 (6.7%) ≥ Gr. 3 decrease platelet count
- 3/30 (10%) ≥ Gr. 3 decrease neutrophil count

No patients had a serious adverse event that was considered related to VAL-083 treatment

Table 4: Number of patients who had a dose reduction (DR) during treatment with VAL-083

At least 1 dose reduction	8 (30.8%)
1 dose reduction	6 (23.1%)
2 dose reductions	2 (7.7%)
Dose reduction - VAL-083 in combination with bevacizumab	2/10 (20.0%)
Dose reduction – after prior lomustine	2/13 (15.4%)

- Thirteen (13/30; 43.3%) of patients had received prior lomustine: 3 patients experienced platelet decreases (one Grade 1, one Grade 2, one Grade 3).
- Ten (10/30; 33%) of patients received bevacizumab with VAL-083: five experienced myelosuppression, decreases in platelet (two Grade 3 or higher) or neutrophil count (one Grade 3).

Patient Outcomes

Table 5: Progression Free Survival (PFS) months from last PD prior VAL-083

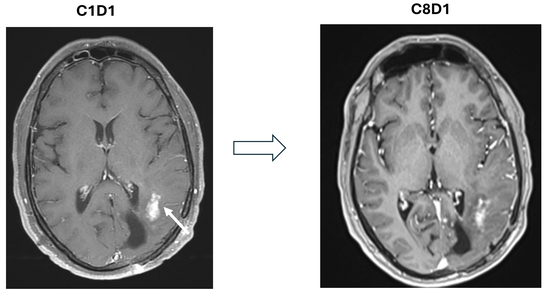
	Number PD, N=26 (%)	PFS (95%CI)
All patients	25/26 (96.2%)	5.1 (2.7-7.2)
Multifocal	10/10 (100%)	2.0 (0.7-7.3)
Non-multifocal	15/16 (93.8%)	5.1 (3.9-7.2)
VAL-083 alone	17/18 (94.4%)	4.8 (2.7-7.2)
VAL-083 + bevacizumab	8/8 (100%)	5.4 (1.3-7.9)
No prior lomustine	16/17 (94.1%)	6.3 (2.0-7.4)
Prior lomustine	9/9 (100%)	3.9 (0.7-5.7)
TERT negative	10/11 (90.1%)	5.7 (2.0-7.3)
TERT positive	15/15 (100%)	5.1 (1.5-7.2)
PTEN negative	15/16 (93.8%)	5.1 (2.7-7.2)
PTEN positive	10/10 (100%)	4.1 (1.1-7.4)

Table 6: Overall Survival (OS) months from last PD prior to VAL-083

	Deaths, N= 26 (%)	OS (95%CI)
All patients	19/26 (73.1%)	9.8 (5.3-16.4)
Multifocal	9/10 (90%)	3.1 (1.7-10.0)
Non-multifocal	10/16 (62.5%)	14.3 (5.3-21.0)
VAL-083 alone	11/18 (61.1%)	14.3 (5.3-19.2)
VAL-083 + bevacizumab	8/8 (100%)	7.6 (3.0-10.0)
Prior lomustine	6/9 (66.7%)	8.3 (2.1-9.8)
No prior lomustine	13/17 (76.5%)	14.3 (5.3-19.2)
TERT negative	5/11 (45.5%)	15.4 (3.9-15.4)
TERT positive	14/15 (93.3%)	7.6 (3.0-14.3)
PTEN negative	11/16 (68.8%)	9.8 (5.3-15.4)
PTEN positive	8/10 (80.0%)	6.7 (1.7-21.0)

Kaplan-Meier Analysis - MedCalc. Ver 23.0.2

Case Study: 58-year-old man with left parietal WHO grade 4 GBM, IDH-WT, pMGMT unmethylated. Status post resection, chemoradiation and 12 cycles of adjuvant temozolomide. At disease progression, he started VAL-083. He completed 8 cycles of VAL-083, with no dose reductions and neurologically stable. MRI after 8 cycles showed mild radiographic improvement.



Conclusions

- Patients can continue treatment with dose reductions of VAL-083 and receive clinical benefit.
- Patients can transition from prior therapies, and with monitoring, continue to receive bevacizumab without significant adverse events
- Use of VAL-083 continues to show benefit in the treatment of GBM patients who have had multiple recurrences and have limited therapeutic options.