VAL-083 in Patients with Recurrent Glioblastoma Treated under Expanded Access Program

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Background

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 overall survival of 3-9 mo. after 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 24 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 N^7-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 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.[3, 4, 5]
- VAL-083 has been studied in phase 2 clinical studies for MGMT-unmethylated recurrent GBM[6], as adjuvant therapy in newly diagnosed MGMT-unmethylated GBM[6], and in combination with radiation therapy in newly diagnosed MGMT-unmethylated GBM patients.[1,2]

Expanded Access Program and Patient Treatment

- Individual patients requested to access VAL-083 under Kintara Therapeutic's 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 2022.
- EA patients received VAL-083 (30 mg/m^2) on day 1, 2 and 3 of a 21-day treatment cycle.

Table 1: Treatment with VAL-083

Number of GBM patients treated under EA	24
Number of GBM patients with leptomeningeal disease (LMD)	4
Number of GBM patients treated under EA (evaluated for efficacy)	20

While safety data was assessed for all patients, those without LMD (20 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)	20
Mean age yrs (range)	54.3 (37-67)
Sex (male)	15 (75%)
Median KPS (95%CI)	80 (70-90)
Number of patients with only 1 recurrence	12 (60%)
Number of patients with >1 recurrence	8 (40%)
Number of patients with >2 recurrence	3 (15%)
Number of patients with multifocal disease	9 (45%)
Number of patients with prior adjuvant temozolomide	15 (75%)
Median number of prior cycles of temozolomide (range)	5 (0-24)
Number patients with prior lomustine	5 (25%)
Median number of prior cycles of lomustine (range)	1 (0-6)
Number of patients receiving concurrent bevacizumab	6 (35%)
Median time from diagnosis (GBM) to start of VAL-083 (mo)	8.4 (5.9-13.5)
Median time from last PD to start of VAL-083 (mo)	0.65 (0.32-1.55)

Table 3: Biomarker Status of Patients Treated under EA (N=20)

MGMT–unmethylated	18 (90%)	EGFR	4 (20%)
IDH WT	18 (90%)	EGFRamp	3 (15%)
TERT	11 (55%)	NF1	4 (20%)
PTEN	9 (45%)	CDKN2A	3 (15%)
TP53	6 (30%)	ARTX	2 (10%)

Safety

Myelosuppression was the primary adverse event

- 2/24 (8.3%) ≥ Gr. 3 decrease platelet count
- 1/24 (4.1%) ≥ 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 VAL-083

At least 1 dose reduction	8/24 (33.3%)
1 dose reduction	6/24 (25.0%)
2 dose reductions	2/24 (8.3%)
Dose reduction - VAL-083 in combination with bevacizumab	4/9 (66.6%)
Dose reduction – after prior lomustine	3/8 (37.5%)

Patient Status

The median number of cycles of VAL-083 received by patients (17/24) was 3.0, with a range of 1-18 cycles. Ten patients (10/24; 41.6%) had 4 or more cycles of VAL-083.

2/24 (8.3%) patients received lomustine after PD on VAL-083. One received 7 cycles of VAL-083, and one 8 cycles of VAL-083, and OS was 13.0 and 7.5 months from start of VAL-083, respectively.

Patient Outcomes

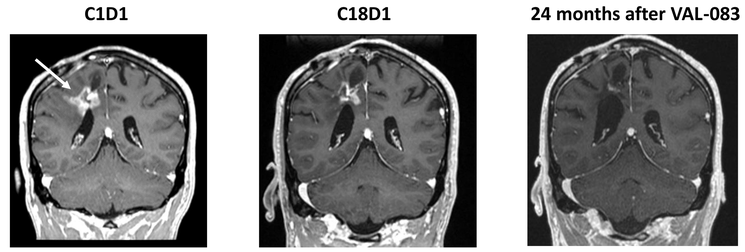
Table 5: Progression Free Survival (PFS) months from last PD prior VAL-083

	Number PD, N=20 (%)	PFS (95%CI)
All patients	15 (75%)	5.8 (2.7-7.8)
Multifocal	7 (78%)	7.1 (0.7-7.8)
Non-multifocal	8 (73%)	5.8 (2.7-19.5)
VAL-083 alone	9 (64%)	7.1 (2.0-12.0)
VAL-083 + bev	6 (100%)	5.6 (1.2-19.5)
Prior lomustine	5 (100%)	3.6 (0.7-5.6)
No prior lomustine	10 (67%)	7.2 (2.7-19.5)
TERT -ve	7 (78%)	3.9 (0.7-7.2)
TERT +ve	8 (73%)	7.1 (1.2-12.0)
1 recurrence	8 (67%)	7.2 (2.0-19.5)
>1 recurrence	7 (88%)	3.6 (0.7-5.6)

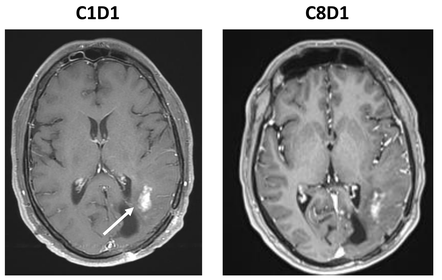
Table 6: Overall Survival (OS) months from last PD prior to VAL-083

	Deaths, N= 20 (%)	OS (95%CI)
All patients	13 (65%)	9.4 (3.9-16.4)
Multifocal	8 (89%)	8.3 (1.7-10.0)
Non-multifocal	5 (45%)	19.2 (3.9-21.0)
VAL-083 alone	8 (57%)	14.3 (2.1-19.2)
VAL-083 + bev	5 (83%)	8.3 (3.0-21.0)
Prior lomustine	4 (80%)	3.9 (2.1-21.0)
No prior lomustine	9 (60%)	14.3 (7.6-21.0)
TERT -ve	4 (44%)	9.4 (2.1-9.4)
TERT +ve	9 (82%)	10 (2.0-19.2)
1 recurrence	7 (58%)	16.4 (7.6-21.0)
>1 recurrence	6 (75%)	3.9 (1.7-10.0)

Case 1. 42-year-old male with right parietal WHO grade 4 GBM, IDH-WT, MGMT promoter unmethylated. Status post resection, chemoradiation and 12 cycles of adjuvant temozolomide. At disease progression, he started on VAL-083 completing 18 cycles. No evidence of disease to date.



Case 2. 59-year-old male with left periatrial white matter WHO grade 4 GBM, IDH-WT, MGMT promoter unmethylated. Status post resection, chemoradiation and 12 cycles of adjuvant temozolomide. At disease progression, he started on VAL-083. Currently on cycle 8 with mild radiologic improvement.



Conclusions

- Consistent with prior clinical studies, myelosuppression is the most common adverse event with VAL-083 in patients with recurrent GBM treated under EA.
- Patients can continue treatment with dose reductions of VAL-083 and receive clinical benefit.
- Patients were able to transition to lomustine as a follow-on therapy after disease progression with VAL-083, without any hematological adverse events.