Abstract # DDDR-36

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 radiation with concurrent and adjuvant temozolomide. There are limited treatment options available upon progression or recurrence of disease. Options often involve participation in clinical trials with promising new therapies. However, patients may not meet the strictly defined entry criteria to participate in these clinical trials.

Here we report on 14 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 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 maintains cytotoxic activity in cancer cells deficient in DNA mismatch repair (MMR).[2,3] 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.[1,2,3]
- VAL-083 has been studied in phase 2 clinical studies MGMT-unmethylated recurrent GBM, recurrent setting[4], as adjuvant therapy in newly diagnosed MGMT-unmethylated GBM[4], and in combination with radiation therapy in newly diagnosed MGMT-unmethylated GBM patients[5,6].

Expanded Access Program And Patient Treatment

- Individual patients requested to access VAL-083 under Kintara Therapeutics Inc Expanded Access (EA) Program. Authorization to proceed with treatment was received US Food and Drug Administration (USFDA) and MD Anderson Cancer Center Institutional Review Board.
- Patients treated under the EA program had recurrent GBM and were enrolled between January 2020 and March 2022.
- EA patients received VAL-083 on day 1, 2 and 3 of a 21-day treatment cycle.

Table 1: Treatment with VAL-083

Starting dose	30 mg/m^2 (100%)
Number co-admin with bevacizumab (Bev)	5 (35.7%)
Number co-admin with dexamethasone (Dex; >4mg)	8 (57.1%)
Number co-admin Bev + Dex	5 (35.7%)
Median cycles of VAL-083 completed	4 (range 1-18)

References

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

Patient Demographics

Table 2: EA Patient Demographics

Number of patients treated under EA	14
Mean age yrs (range)	56 (37-67)
Sex (male)	10 (71.4%)
Median KPS	80 (range 50-90)
Number of patients KPS≥70	12 (85.7%)
Number of patients KPS<70	2 (14.3%)
Number of patients with only 1 recurrence	9 (64.3%)
Number of patients with >1 recurrence	5 (35.7%)
Number of patients with multifocal disease	8 (57.1%)
Number patients with prior lomustine	3 (21.4%)
Number of patients with adjuvant temozolomide	9 (64.3%)
Median time from diagnosis (GBM) to start of VAL-083 (mo)	8.4 (CI: 4.2-13.1)
Median time from last PD to start of VAL-083 (mo)	1.0 (CI: 0.1-2.7)

Table 3: Biomarker Status of Patients Treated under EA

MGMT–unmethylated	14 (100%)	EGFR	4 (28.6%)
IDH WT	13 (92.3%)	PTN11	2 (14.3%)
TERT	9 (64.3%)	PIK3CA	2 (14.3%)
PTEN	6 (42.9%)	NF1	2 (14.3%)
TP53	5 (35.7%)	CDKN2A	2 (14.3%)

Safety

Myelosuppression was the primary adverse event

- 3/14 (21.4%) Gr. 1 decrease platelet counts, 1/14 (7.1%) Gr. 4 decrease platelet count*
- 1/14 (7.1%) Gr. 3 decrease neutrophil count, 1/14 (7.1%) Gr. 4 decrease neutrophil count

* Patient had prior treatment with lomustine, AE occurred during cycle 3 VAL-083.

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

At least 1 dose reduction	4/14 (28.6%)
1 dose reduction	2/14 (14.3%)
2 dose reductions	2/14 (14.3%)
Dose reduction - VAL-083 in combination with bevacizumab	0/5 (0%)

Patient Status

The median number of cycles of VAL-083 received by patients was 4, with a range of 1 to 18 cycles. Eight (8/14; 57% had 4 or more cycles of VAL-083.

2/14 (14.3%) patients received lomustine after PD on VAL-083, and continued treatment without adverse hematological adverse events

Treatment Outcomes

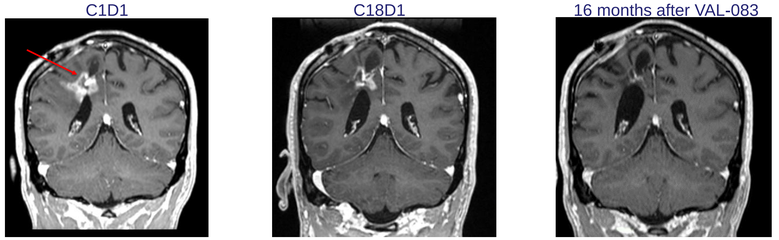
Table 5: Progression Free Survival (PFS) months from last PD prior to starting VAL-083

	Number PD (%)	PFS (95%CI)
All patients	13/14 (92.9%)	5.7 (1.3-7.9)
Multifocal	8/8 (100%)	3.1 (0.7-7.3)
Non-multifocal	5/6 (83.3%)	5.9 (3.9-19.8)
VAL-083 alone	8/9 (88.9%)	4.8 (0.7-12.2)
VAL-083 + bev	5/5 (100%)	5.9 (1.3-19.8)
TERT -ve	4/5 (80.0%)	5.7 (0.7-7.3)
TERT +ve	9/9 (100%)	5.9 (0.8-12.2)
1 recurrence	8/9 (88.9%)	7.2 (0.8-19.8)
>1 recurrence	5/5 (100%)	3.9 (0.7-7.9)

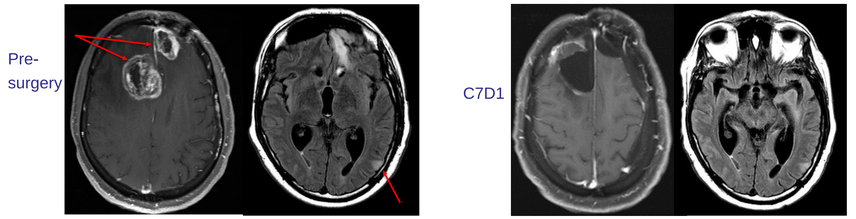
Table 6: Overall Survival (OS) months from last PD prior to starting VAL-083

	Number OS (%)	OS (95%CI)
All patients	10/14 (71.4%)	8.3 (3.0-14.3)
Multifocal	7/8 (87.5%)	4.2 ((2.0-10.0)
Non-multifocal	3/6 (50.0%)	14.3 (3.9-14.3)
VAL-083 alone	6/9 (66.7%)	9.4 (2.0-14.3)
VAL-083 + bev	4/5 (80.0%)	8.3 (3.0-10.0)
TERT -ve	4/5 (80.0%)	8.3 (2.1-9.4)
TERT +ve	6/9 (71.4%)	10.0 (4.0-14.3)
1 recurrence	5/9 (55.6%)	14.3 (2.0-14.3)
>1 recurrence	5/5 (100%)	3.9 (2.1-10.0)

- **Case 1.** 41-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.** 54-year-old male with bifrontal and left temporal WHO grade 4 GBM, IDH-WT, MGMT promoter unmethylated. Status post resection, chemoradiation with concurrent temozolomide. He underwent re-resection (confirming early recurrence) and started VAL-083, he completed 7 cycles. He stopped treatment for reasons unrelated to VAL-083.



Conclusion

- Consistent with prior clinical studies, myelosuppression is the most common adverse event with VAL-083 in patients with recurrent GBM treated under EA
- Patients were able to receive VAL-083 in combination with bevacizumab without any hematological adverse events
- Patients were able to transition to lomustine as a follow-on therapy after disease progression with VAL-083, without any hematological adverse events