RELA Fusion-positive Ependymoma, Diffuse Midline Glioma And WHO grade 4 IDH Mutant Astrocytoma Treated With VAL-083 Under Expanded Access: Case Reports

Carlos Kamiya-Matsuoka[1], Shiao-Pei Weathers[1], Stephanie Knight[1], Teresa Hanna[1], John Langlands[2], Dennis Brown[2], Vinay Puduvalli[1]

[1]Department of Neuro-Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; [2]Valent Technologies, LLC, Menlo Park, CA, USA

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Introduction

RELA fusion-positive ependymoma is associated with supratentorial location, higher WHO grade and poor prognosis. Diffuse Midline Glioma (DMG) is a relatively rare CNS tumor, originating in the midline location of the brain. Surgical intervention is restricted to biopsy and radiation. WHO grade-4 astrocytoma, is highly aggressive with rapid progression. Standard treatment includes surgery and radiation therapy, with limited systemic options other than clinical trials for recurrent disease.

VAL-083 is a DNA-targeting agent which rapidly induces inter-strand DNA cross-links at O6- and N7-guanine inducing double-strand breaks causing cell death and acts independent of MGMT DNA repair in high-grade gliomas.[1,2,3,4]

We report on 4 patients who had recent disease progression and unmethylated MGMT promoter status treated with VAL-083 under an expanded access program:

- Case #1: a 47-yo male diagnosed with IDHwt, RELA fusion-positive ependymoma.
- Case #2: an 18-yo male diagnosed with IDHwt, MAP2K1 and RELA fusion-positive ependymoma.
- Case #3: a 25-yo male diagnosed with IDHmut WHO grade 4 astrocytoma, with ATRX, INPP4A, RET and TP53 mutations.
- Case #4: a 21 yo male diagnosed with IDHwt DMG of the brain stem.

Expanded Access Program

- 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 October 2022 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.

Conclusions

- VAL-083 was well tolerated in these patients after prior medications including lomustine.
- No dose reductions were required.
- These cases highlight that VAL-083 may be a treatment option for recurrent RELA fusion-positive ependymoma, WHO grade 4. IDHmut astrocytoma, and DMG refractory to other treatment regimens.

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

Case #1 – Ependymoma, WHO grade 3

47-yo male, IDHwt, ZFTA (RELA fusion) mutation, MGMT promoter unmethylated

Prior Treatments:

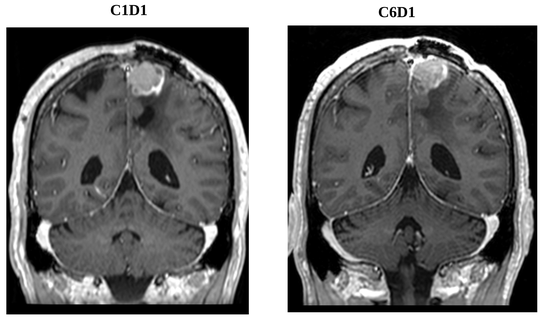
- Chemoradiation with temozolomide; adjuvant temozolomide with lapatinib (5 cycles); nivolumab
- Two recurrences prior to starting VAL-083
- KPS = 80 at start of treatment with VAL-083

Treatment

- Cycles of VAL-083 received: 6 cycles at 30 mg/m^2/d x 3 days every 21 days
- No dose reductions during treatment

Outcomes

- Time to progression on VAL-083 (from start of VAL-083) – 4.1 months
- Survival from start of treatment with VAL-083 – 24.1 months (last date known alive)



Case #2 – Ependymoma, WHO grade 3

18-yo male, IDHwt, MAP2K1 and ZFTA (RELA fusion) mutation, MGMT promoter unmethylated

Prior Treatments:

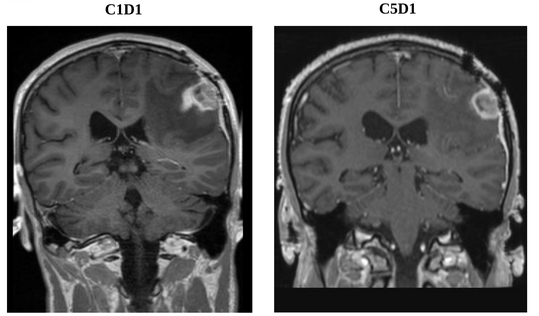
- Chemoradiation with temozolomide; adjuvant temozolomide (4 cycles); nivolumab, bempegaldesleukin, lapatinib and temozolomide
- Three recurrences prior to starting VAL-083
- KPS = 80 at start of treatment with VAL-083

Treatment

- Cycles of VAL-083 received: 5 cycles at 30 mg/m^2/d x 3 days every 21 days
- No dose reductions during treatment

Outcomes

- Time to progression on VAL-083 (from start of VAL-083) – 4.2 months
- Survival from start of treatment with VAL-083 – 12.1 months (last date known alive)



Case #3 – Astrocytoma, WHO grade 4

25-yo male, IDHmt, ATRX, IDH2, INPP4A, RET, TP53 mutations, MGMT promoter unmethylated

Prior Treatments:

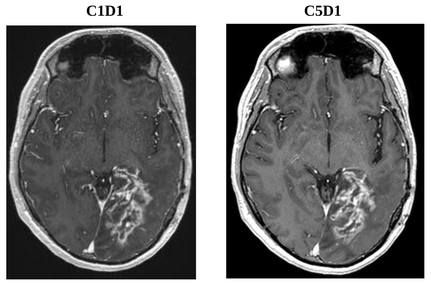
- Chemoradiation with temozolomide; adjuvant temozolomide (12 cycles); lomustine (3 cycles), proton radiation
- Three recurrences prior to starting VAL-083
- KPS = 90 at start of treatment with VAL-083

Treatment

- Cycles of VAL-083 received: 5 cycles at 30 mg/m^2/d x 3 days every 21 days
- No dose reductions during treatment

Outcomes

- Time to progression on VAL-083 (from start of VAL-083) – 3.9 months
- Survival from start of treatment with VAL-083 – 14.1 months (last date known alive)



Case #4 – Pontine Glioma (Diffuse Midline Glioma)

21-yo male, IDHwt, no mutations, MGMT promoter unmethylated

Prior Treatments:

- Chemoradiation with temozolomide; adjuvant temozolomide (12 cycles); lomustine (3 cycles), bevacizumab
- Three recurrences prior to starting VAL-083
- KPS = 100 at start of treatment with VAL-083

Treatment

- Cycles of VAL-083 received: 18 cycles at 30 mg/m^2/d x 3 days every 21 days
- VAL-083 concurrent with bevacizumab
- No dose reductions during treatment

Outcomes

- Time to progression on VAL-083 (from start of VAL-083) – 13.8 months
- Survival from start of treatment with VAL-083 – 16.9 months