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Background

Ependymoma can occur anywhere in the central nervous system (CNS), but often occurs near the ventricle of the brain and central canal of the spinal cord. Ependymoma accounts for 5.7% of all childhood and 1.9% of all adult CNS tumors. RELA fusion-positive ependymoma is a subgroup associated with supratentorial location, higher WHO grade and worse prognosis. Diffuse Midline Glioma (DMG) is another relatively rare CNS tumor, originating in the midline locations of the brain (including thalamus, pons and spinal cord), accounting for 10% of all childhood and less than 4% of adult CNS tumors. For ependymoma, standard treatment includes surgery and radiation therapy, with limited systemic options other than clinical trials for recurrent disease. For DMG, surgical intervention is restricted to biopsy, with radiation as standard therapy. Systemic options for both ependymoma and DMG are limited.

Here we report on two patient cases treated with VAL-083 under expanded access (EA):

- **Recurrent RELA fusion-positive ependymoma**
- **Recurrent diffuse midline glioma**

About VAL-083

- **VAL-083** is a CNS penetrating^{1,2} and DNA targeting agent that rapidly induces interstrand cross-links at 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, 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 GBM⁶, as adjuvant therapy in newly diagnosed MGMT-unmethylated GBM⁶, and in combination with radiation therapy in newly diagnosed MGMT-unmethylated GBM patients.^{1,2}

Expanded Access Program

- The individual patients requested to access VAL-083 under Kintara Therapeutic's Expanded Access (EA) program.
- Treatment plans were reviewed and 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 were not eligible for any clinical trials.
- Clinicaltrials.gov Identifier: NCT03138629

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

RELA Fusion-Positive Ependymoma

Patient Medical History

- 48-year old male, with left frontoparietal WHO grade III ependymoma
- Inter- and intragenic fusion analysis of tumor tissue revealed C11orf95-RELA fusion, diagnosis of RELA fusion-positive ependymoma was established
- No somatic mutations identified, including IDH1 and IDH2 genes
- Unmethylated MGMT promoter
- Time from initial diagnosis to start of treatment with VAL-083 was 16 years
- Karnofsky performance score was 80
- Gross total resection, followed by chemoradiation and adjuvant TMZ with lapatinib (5 cycles). Most recent treatment before VAL-083 included immunotherapy
- Patient had 2 recurrences prior to initiation of treatment with VAL-083

Patient Treatment and Safety

Treatment

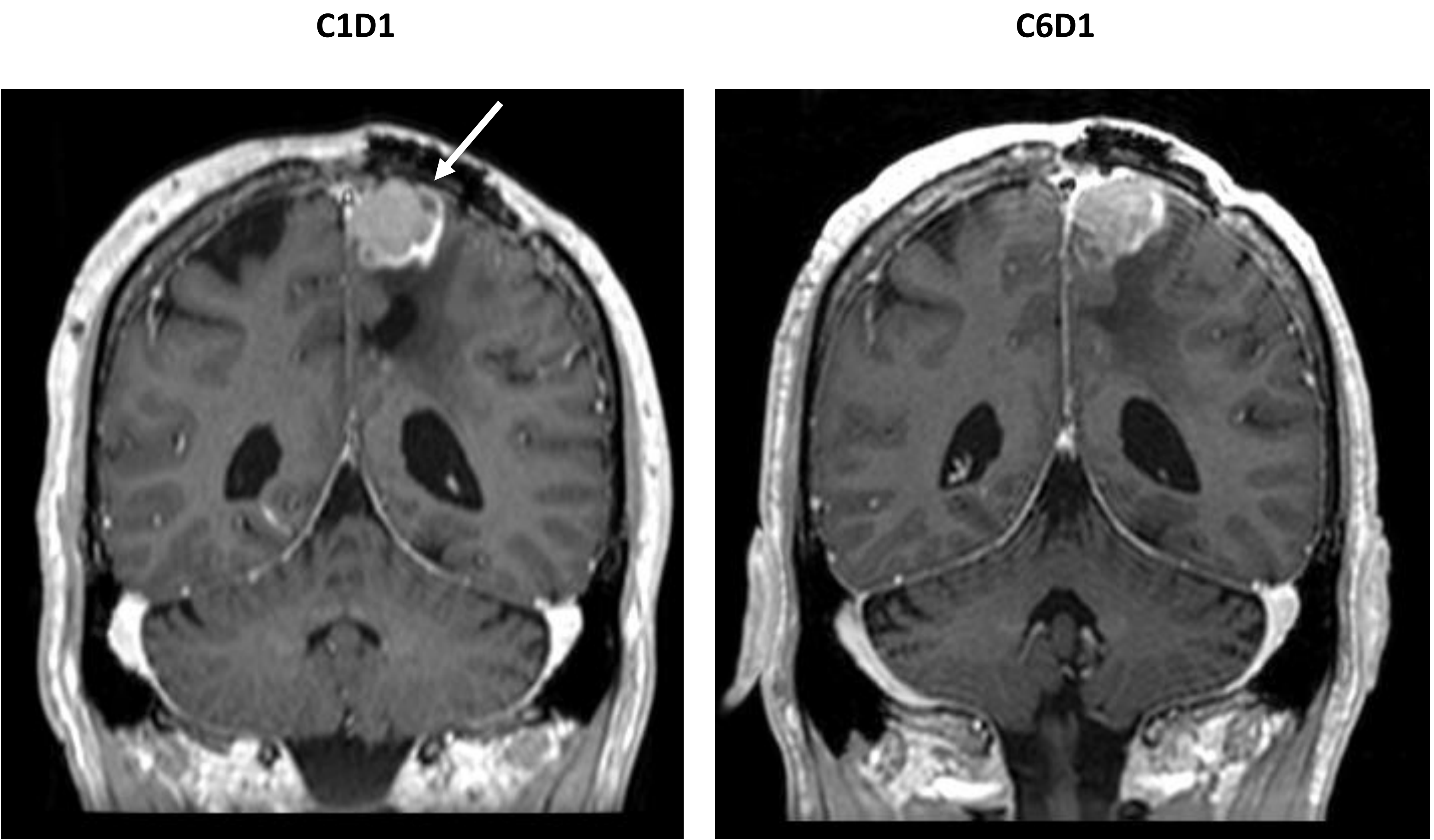
- VAL-083 30 mg/m² on days 1, 2 and 3 of a 21-day cycle
- 6 cycles have been completed, and treatment is continuing [data cut-off 31 March 2023]

Safety

- No adverse events have been reported
- No grade 3/4 adverse events such thrombocytopenia, anemia, neutropenia, or lymphopenia
- No dose reductions during the course of treatment with VAL-083

Patient Outcomes

- No progression of disease identified in the left frontoparietal tumor by cycle 6



Diffuse Midline Glioma

Patient Medical History

- 21-year old male, with diffuse midline glioma of the pons
- No somatic mutations identified, including H3F3A, IDH1 and IDH2 genes
- Unmethylated MGMT promoter
- Karnofsky performance score was 60
- Time from initial diagnosis to start of treatment with VAL-083 was 28.9 months
- Patient had 3 recurrences prior to initiation of treatment with VAL-083
- **Gross total resection, followed by chemoradiation** and adjuvant TMZ (12 cycles)
- Patient received prior CCNU (3 cycles) and bevacizumab (2 cycles) prior to VAL-083
- Patient continued to receive bevacizumab (10 mg/kg) with VAL-083

Patient Treatment and Safety

Treatment

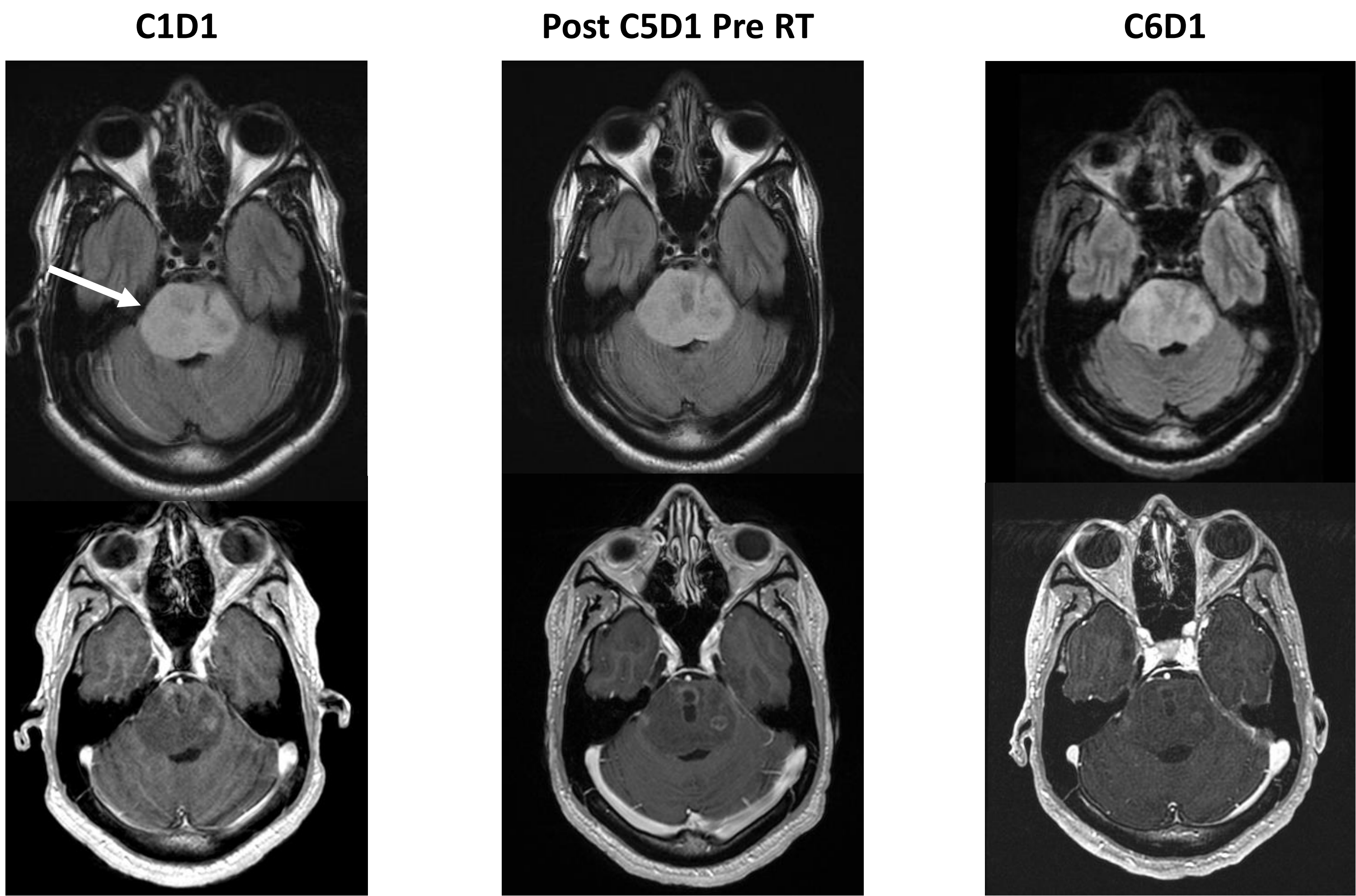
- VAL-083 30 mg/m² on days 1, 2 and 3 of a 21-day cycle
- 5 cycles completed of treatment were completed without dose reduction
- Patient underwent radiation therapy (24 Gy over 12 fractions)
- VAL-083 was resumed after radiation therapy and the patient completed 1 additional cycle

Safety

- No adverse events were reported
- No grade 3/4 hematological adverse events
- No dose reductions during the course of treatment with VAL-083
- No adverse interactions during co-administration of VAL-083 with bevacizumab

Patient Outcomes

- No progression of disease identified by cycle 6



Conclusions

These cases highlight that VAL-83 may be a treatment option for recurrent RELA fusion-positive ependymoma refractory to temozolomide-based regimens and for recurrent diffuse midline glioma.