Abstract # DDDR-34

Recurrent RELA Fusion-Positive Ependymoma Treated with VAL-083 under Expanded Access: A Case Report

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Background

Ependymoma is a relatively rare central nervous system tumor accounting for 2-9% of all neuroepithelial tumors. RELA fusion-positive ependymoma is a subgroup associated with supratentorial location, higher WHO grade and worse prognosis. In addition, there is no standard systemic chemotherapy treatment for adults with recurrent disease. With limited treatment options available for patients, VAL-083 offers a suitable treatment alternative.

Here we report a patient case with recurrent RELA fusion-positive ependymoma was treated with VAL-083 under expanded access (EA).

About VAL-083

- **VAL-083** is a novel bi-functional DNA targeting agent that rapidly induces inter strand 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

- The individual patient requested to access VAL-083 under Kintara Therapeutics Inc Expanded Access (EA) Program.
- Treatment plans were reviewed and Authorization to Proceed with treatment was received from US Food and Drug Administration and MD Anderson Cancer Center Institutional Review Board.
- Patient was not eligible for any clinical trials, treated under EA program.
- Clinicaltrials.gov Identifier: NCT03138629

References

1: Zhai B, et al. Cell Death and Disease. (2018)9:1016; 2: Zhai B, et al. Cancer Res. July 2017: 77(13), abstract #248; 3: Fouse S, et al. Neuro Oncol. (2014). v16(Supll 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 Medical History

- 40-year old male, initially diagnosed with right parieto-occipital high-grade glioma.
- No somatic mutations, including IDH1/2 genes.
- Unmethylated MGMT promoter
- Gross total resection, followed by chemoradiation and adjuvant temozolomide (12 cycles)
- 16 months after initial treatment completed, disease recurrence and second resection was performed
- Inter- and intragenic fusion analysis of tumor tissue revealed C11orf95-RELA fusion

➢ Diagnosis of RELA fusion-positive ependymoma was established

Patient Treatment & Safety

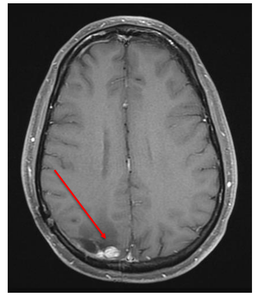
Treatment
- VAL-083 30 mg/m^2 on days 1, 2 and 3 of a 21-day cycle
- 12 cycles completed over 9-month period

Well tolerated
- Liver and renal function remained normal
- No grade 3/4 adverse events such thrombocytopenia, anemia, neutropenia, or lymphopenia
- No dose reductions during the course of treatment with VAL-083

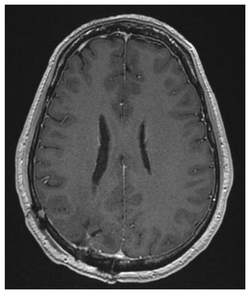
No drug-drug interactions
- Patient received levetiracetam, alprazolam and prochlorperazine, and no adverse effects or dose adjustments were required

Patient Outcomes

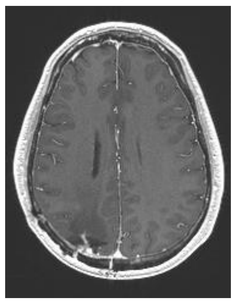
- This MRI of brain showed progressive nodular enhancement in the right occipital lobe after treatment with temozolomide. Patient developed left visual field deficit.



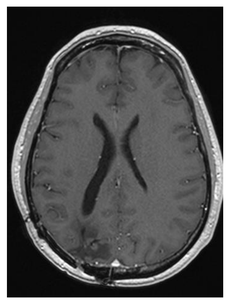
- He underwent right occipital craniotomy with gross total resection of the tumor.
- Pathology reported WHO grade 3, RELA fusion-positive ependymoma.



- 8 weeks after second resection, nodular enhancement was noticed in the operative site suggesting tumor progression.
- He started on VAL-083 (30 mg/m^2/day) and completed 12 cycles



- 18 months after completion of treatment with VAL-083, the patient remains neurologically and radiologically stable with no evidence of disease.



Summary and Conclusions

- VAL-083 was well tolerated with no significant adverse events and no dose reductions required.
- The patient continues to remain stable with no evidence of disease 18 months after completion of 9 cycles of VAL-083.
- This case highlights that VAL-83 may be a treatment option for recurrent RELA fusion-positive ependymoma refractory to temozolomide-based regimens.