VAL-083 inhibits proliferation of a panel of eight glioblastoma stem cells: Downregulation of BRD4 as a novel anti-neoplastic mechanism

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Introduction

VAL-083 (Dianhydrogalactitol) is a bi-functional DNA targeting agent that is currently being evaluated in a phase II trial in recurrent glioblastoma (GBM) patients. A key feature of VAL-083 that distinguishes it from temozolomide, is that it is effective against GBMs with both methylated and unmethylated MGMT promoter. The goal of the present study was to further elucidate the anti-neoplastic effects and signaling pathways through which VAL-083 functions.

Methods

We examined the efficacy of VAL-083 against a panel of eight GBM stem cells (GSCs) isolated from newly diagnosed GBM patients. The panel of GSCs were molecularly phenotyped, based on the expression of several proteins, including EGFR, EGFRvIII, and MGMT as well as several stem cell markers including SOX2, NESTIN, MST1, CD133, TFRC, and OLIG2. The effect of VAL-083 on GSC growth was measured using WST-1 reagent, while the effect on the GSC's ability to form neurospheres was assessed by microscopy.

Results

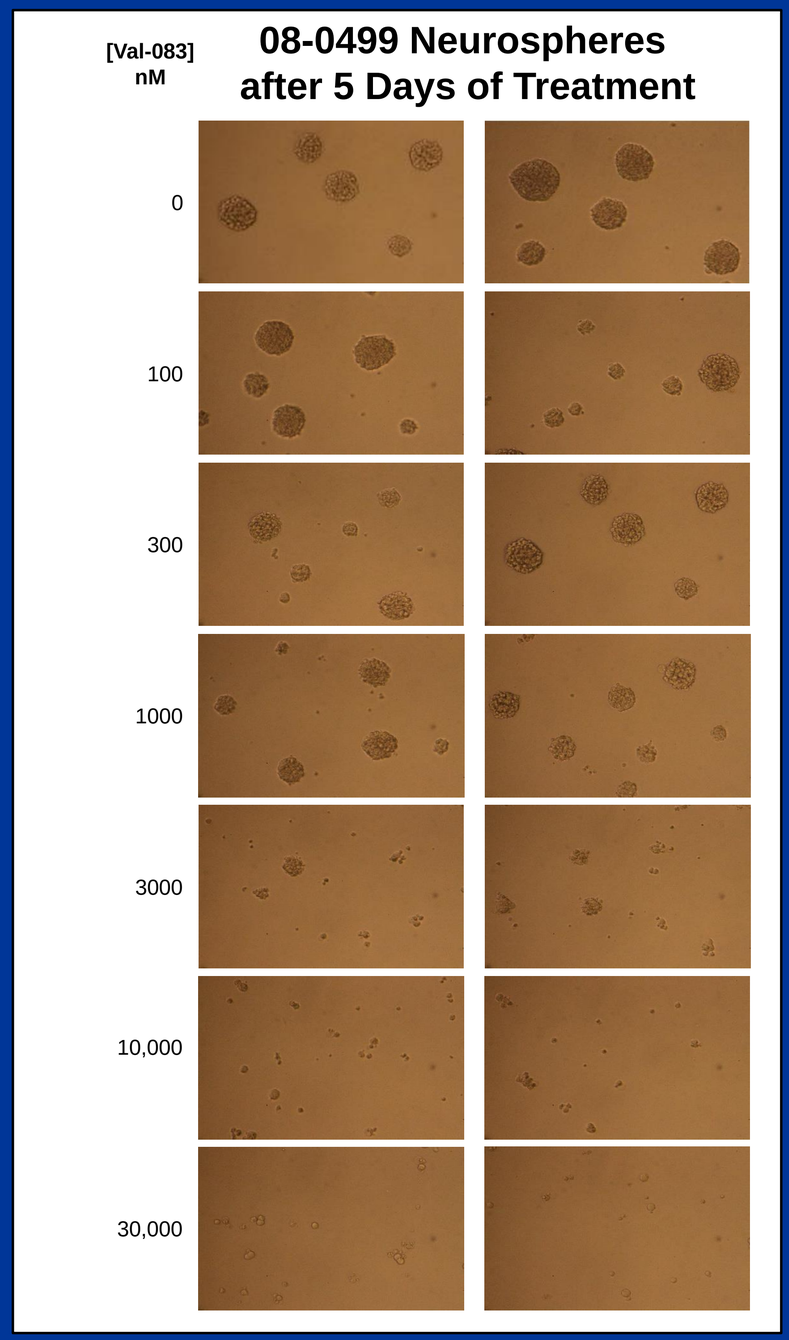
Our cell viability assay results show that VAL-083 inhibits neurosphere formation in all eight GSCs. Efficacy in 08-0499 neurospheres is shown in the panel to the right. Further, VAL-083 inhibits the growth of various GSCs with an IC_{50} ranging from 200-2000 nM suggesting specificity and the need for a precision-based trial.

Figure 1 shows the effect of different concentrations of VAL-083 on neurosphere formation in GSC 08-0499. An effect of on neurosphere inhibition is clearly seen at 3uM VAL-083.

Analysis of control and VAL-083-treated GSC 08-0499 by Reverse Phase Protein Array (RPPA) approach revealed changes in several proteins including a greater than 100% decrease in BRD4, This is an interesting finding because BRD4 is overexpressed in GBM and disruption of its expression reduces cell cycle progression.

Conclusion

VAL-083 inhibits the growth of GBM stem cells, and the mechanism may involve a downregulation of BRD4.



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