Dianhydrogalactitol (VAL-083) reduces glioblastoma tumor progression in vivo, upon bevacizumab-induced hypoxia

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Standard-of-care for glioblastoma (GBM) includes surgery, radiation and temozolomide. Nearly all tumors recur and 5-year survival is less than 3%. Unmethylated promoter status O6-methylguanine-DNA-methyltransferase (MGMT) is a validated biomarker for temozolomide-resistance. Second-line treatment with bevacizumab has not only failed to improve survival, but has also been shown to induce intratumor hypoxia and increased chemoresistance. VAL-083 is a bi-functional DNA-targeting agent that readily crosses the blood-brain barrier. VAL-083 targets N7-guanine, causing DNA double-strand breaks and cancer cell-death in GBM cancer stem cells (CSCs) and non-CSCs, independent of MGMT. To investigate the in vivo anti-tumor effect of VAL-083+bevacizumab, we used an orthotopic GBM T16 PDX model. All mice carried MGMT-unmethylated, temozolomide-resistant recurrent GBM tumors detected by MRI 35 days post-implantation. Tumor progression was measured by MRI on days 49 and 56, and was calculated for the entire study (day 35 vs. 56) and for the last 7 days (day 49 vs. 56). Mice were grouped into control, bevacizumab, VAL-083, and VAL-083+bevacizumab. VAL-083 treatment started 3 days after bevacizumab treatment to ensure induction of hypoxia. Results: Tumors were significantly smaller in VAL-083-treated mice both compared to control (-83%, p<0.001) and compared to bevacizumab-treated (-75%, p<0.001) mice. Additionally, analysis of tumor growth in-time showed significantly reduced tumor progression for VAL-083+bevacizumab compared to VAL-083 alone (p<0.01). Conclusions: These results show strong in vivo anti-tumor efficacy of VAL-083 against MGMT-unmethylated, recurrent GBM. This effect was further augmented in combination with bevacizumab, providing rationale of clinical investigation of VAL-083+bevacizumab in GBM.

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