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VAL083, a novel N7 alkylating agent, surpasses temozolomide activity and inhibits cancer stem cells providing a new potential treatment option for glioblastoma multiforme

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Key words: glioblastoma multiforme, Temozolomide, drug resistance, MGMT, cancer stem cells.

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Abstract

Glioblastoma (GBM) remains one of the most difficult tumors to to treat in part because many new agents fail to cross the blood brain barrier (BBB) and secondly due to intrinsic drug resistance. Temozolomide (TMZ) is a front-line therapy for the treatment of GBM, however, it is often ineffective due to drug inactivation by O^6-methylguanine-DNA methyltransferase (MGMT). Cancer stem cells (CSC) are a subpopulation of the tumor that resist therapy and give rise to relapse. Here we described VAL083 a novel alkylating agent that creates N^7 methylation on DNA, which was initially intriguing because it crosses the BBB. We addressed how it compared to TMZ, whether it could be used to overcome MGMT-driven drug resistance and if has activity against CSCs. Addressing these questions provides further preclinical support for VAL083, which is currently undergoing human clinical trials in the USA against refractory GBM. VAL083 inhibited U251 and SF188 cell growth in monolayer and as neurospheres better then TMZ and caused apoptosis after 72 hrs. In a 10-day colony formation assay, VAL083 (5uM) suppressed SF188 growth by ~95%. T98G cells are classically TMZ resistant and express MGMT yet VAL083 inhibited their growth in monolayer after 72 hrs in a dose-dependent manner (IC50=5 uM). VAL083 also inhibited the growth of CSCs by 100% in neurosphere growth assays. In summary, VAL083 has better in vitro efficacy than TMZ against brain tumor cells, can overcome resistance associated with MGMT, and targets brain tumor CSCs demonstrating that it has the potential to surpass the standard-of-care.