Despite decades of trials, the prognosis for diffuse intrinsic pontine gliomas (DIPG) remains dismal. DIPG is inoperable and standard treatment is radiation alone, as the addition of chemotherapeutic agents, such as temozolomide, have not improved survival. In addition to inherent chemoresistance, treatment of DIPG is impeded by an intact blood-brain barrier (BBB). VAL-083 is a structurally unique bi-functional DNA-targeting agent that readily crosses the BBB. VAL-083 forms interstrand DNA crosslinks at N7-guanine, resulting in DNA double-strand breaks (DSB), S/G2-phase cell-cycle arrest, and ultimately cancer cell death. We have previously demonstrated that VAL-083 is able to overcome temozolomide-resistance in vitro and in vivo, and that its cytotoxicity is independent of the DNA-repair enzyme O6-methylguanine DNA-methyltransferase (MGMT). MGMT is almost universally expressed in DIPG and its expression is strongly correlated with temozolomide-resistance. VAL-083‟s distinct mechanism-of-action suggests the potential for combination with inhibitors of DNA DSB repair or S/G2 cell-cycle progression (e.g. Wee1 inhibitor AZD1775). Here, we investigated the effects of VAL-083 in combination with radiation, AZD1775 or irinotecan (topoisomerase inhibitor) in three DIPG cell-lines: SF10693 (H3.1), SF8628 (H3.3) and NEM157 (H3.3). VAL-083 showed activity at low uM-concentration in all three cell-lines. In addition, VAL-083 showed synergy with AZD1775 in all three cell-lines. Combined with its ability to cross the BBB, accumulate in brain tumor tissue and overcome MGMT-related chemoresistance, these results suggest VAL-083 as a potentially attractive treatment option for DIPG as single agent or in combination with AZD1775. Combination studies with radiation are ongoing and will be presented at the meeting.

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Phase 2 studies of dianhydrogalactitol (VAL-083) in patients with glioblastoma, MGMT-unmethylated

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Current standard-of-care for glioblastoma (GBM) includes surgery, radiation and temozolomide. Most tumors recur within a year from diagnosis and median survival for recurrent GBM (rGBM) is 3-9 months. Unmethylated promoter status for O6-methylguanine-DNA-methyltransferase (MGMT) is a validated biomarker for temozolomide-resistance, exhibited by most GBM patients. VAL-083 is a DNA-targeting agent with a mechanism-of-action that is independent of MGMT. VAL-083 overcomes temozolomide-resistance in GBM cell-lines, cancer stem cells, and in vivo models. VAL-083 readily crosses the blood-brain barrier and accumulates in brain-tumor tissue. We recently completed a VAL-083 dose-escalation trial in temozolomide- and bevacizumab-refractory rGBM and determined that 40mg/m2/day given intravenously on days 1,2,3 of a 21-day cycle is generally well-tolerated. This dosing regimen was selected for subsequent GBM trials, including an ongoing single-arm, biomarker-driven Phase 2 trial (N=48) in temolozomide-refractory, bevacizumab-naïve rGBM , MGMT-unmethylated (Clinicaltrials.gov:NCT02717962). The primary objective of this study is to determine if VAL-083 improves OS compared to a historical control of 7.15 months for MGMT-unmethylated rGBM patients treated with lomustine (EORTC26101). In addition, another single-arm, biomarker-driven, Phase 2 study (N=25) of VAL-083 in combination with radiotherapy in newly diagnosed GBM, MGMT-unmethylated is ongoing (Clinicaltrials.gov:NCT03050736). This trial aims to determine a dose for further study of VAL-083 in combination with radiotherapy and explore if VAL-083 improves PFS and OS compared to historical results in newly diagnosed GBM. Enrollment and safety data updates will be provided at the meeting. The results of these studies, if successful, may support VAL-083 as part of a new chemotherapeutic treatment paradigm for GBM.

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Are gangliogliomas in children and adults disorders of nervous system development?

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INTRODUCTION: Gangliogliomas (GGs) are neuroepithelial tumours of the central nervous system (CNS) composed of mature ganglion cells or a mixed population of ganglion and glial cells. Microarray data of low grade gliomas (LGG) including GGs revealed overexpression of the Dlx2 gene, a homeobox gene essential for interneuron migration and differentiation. We hypothesized that GGs are arrested in development, and began to explore the role of the Dlx2 gene. BRAF rearrangements and BRAF V600E point mutations have been reported in pediatric LGG. METHODS: DLX2 expression was examined in GGs using immunofluorescence (IF) and immunohistochemistry (IHC) labelling of formalin fixed paraffin embedded (FFPE) tissue sections, along with staining of glial and neuronal markers. BRAF mutations were detected using a commercial antibody and/or sequence verification of the DNA extracted from the FFPE blocks. RESULTS: In the Discovery cohort 10/30 were DLX2+ (33.3%) and in the Validation cohort 15/40 were DLX2+ (37.5%). Of these 15 cases, 15 were GFAP+ (100%), 15 were synaptophysin and/or NeuN+ (100%), and 13 were OLIG2+ (86.7%); 6 had a BRAF V600E mutation (40.0%). For the Validation cohort of 40 GGs, 28 were OLIG2+ (70.0%); 13/28 co-expressed DLX2 (46.4%). 18/40 cases had a BRAF V600 mutation(17 V600E, 1 V600G; 45.0%) and 6/18 were DLX2+ (33.3%). CONCLUSIONS: DLX2 is expressed in GGs in both neuronal and glial marker expressing tumour cells. Our results support that GGs arise from CNS progenitors arrested at the neuronal-glial cell fate “decision” point.

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Functional characterization of ribosomal RNA methyltransferase NSUN5 in glioblastoma

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Glioblastoma is the most common and malignant brain tumor with a median overall survival of 20.5 months. There is an urgent need to develop novel therapeutic strategies. Using a glioblastoma TCGA dataset, we have determined that high NSUN5 mRNA expression is strongly associated with poor survival in glioblastoma patients. NSUN5 is a ribosomal RNA (rRNA)