identify clinically and biologically relevant subgroups within IDH-mutant gliomas to gain a deeper insight into finer sub-classification. Methods: We used 412 IDH-mutant glioma samples that were profiled by The Cancer Genome Atlas (TCGA) Research Network, utilising methylation/mRNA datasets to identify subtypes with unique molecular signatures. We applied a Similarity Network Fusion (SNF) on individual platforms and their integrations. Results: SNF approach split glioma into four groups. The integrated RNA/methylation subtype produced a highly prognostic groups that predict survival (p-value=0.003) compared to mRNA and methylation alone. We observed a high degree of correlation between integrative subtypes and somatic mutations. Groups 1&4 had higher TERT promoter mutations (35% and 16%, respectively) compared to groups 2&3. Groups 1&4 showed increased TERT expression (34% and 14% respectively), and high percentage of TP53 and ATRX mutations. Multivariate analysis after adjusting for confounding factors including grade and age showed prognostic factors associated with survival (HR=3.2, p-value=0.001) in group 4 versus others. Conclusions: The results indicate that clinically relevant alterations exist within IDH-mutant gliomas that could stratify patients for treatment. Interestingly, group 4 showed high expression of HOX genes (18/18) (p-value=0.01) and higher methylation of Hox genes (21) (p-value=0.01) compared to others. Higher expression of specific Hox genes were associated with worse survival.

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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+bevacizmab. 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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Unraveling molecular drivers of brain cancers at the clinical setting

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Brain tumor behavior is driven by aberrations in the genome and epigenome. Many of these changes, such as IDH mutations in diffuse low-grade glioma (DLGG), are common amongst the same class of tumour and can be incorporated into the diagnostic criteria. However, any given tumor may have other, less common genomic aberrations that are essential for its biological behavior and may inform on underlying aberrant cellular pathways, and potential therapeutic agents. Precision oncology is a genomics-based approach which profiles these alterations to better manage cancer patients and has established itself within the practice of oncology and is slowly making its way into neuro-oncology. The BC Cancer˝s Personalized OncoGenomics (POG) program has profiled 16 adult tumours originating from the central nervous system using whole genome and transcriptome analysis (WGTA), for the first time, within a meaningful clinical timeframe/setting. As expected, primary genomic drivers were consistent with their respective diagnoses, though secondary drivers were found to be unique to each tumour. Although these analyses did not result in altered clinical management for these patients, primarily due to availability of drug or clinical trials, they highlight the heterogeneity of secondary drivers in cancers and provide clinicians with meaningful biological information. Lastly, the data generated by POG has highlighted the frequency and complexity of novel driver fusions which are predicted to behave similarly to canonical driver events in their respective tumours. The information available to clinicians through POG has provided paramount knowledge into the biology of each unique tumour.

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Microglia and macrophages display heterogeneous phenotypes in IDH-mutant and -wildtype glioblastomas

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Background: CNS innate immune cells, microglia and macrophages (MMs), are the largest component of the inflammatory infiltrate in glioblastoma (GBM). They initially participate in tumor surveillance, but are subverted by GBM. Immunotherapies have proven incredibly successful in cancers