Phenotypic assessment of the models in vitro by high-throughput imaging demonstrated significantly increased invasion and migration in association with either KMT5B or KMT5C loss, but not both. Quantitative proteomic analysis identified a set of secretome-identified factors by which a minority of KMT5B-deficient cells may signal to promote motility of the neighbouring populations. These data suggest a previously unrecognized trans-histone (H4/H3) interaction in DIPG cells with a potentially profound effect on their diffusely infiltrating phenotype.

DIPG-64. INTERNATIONAL PRECLINICAL DRUG DISCOVERY AND BIOMARKER PROGRAM INFORMATION AN ADAPTIVE COMBINATORIAL TRIAL FOR DIFFUSE MIDLINE GLIOMAS

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INTRODUCTION: DMG-ACT (DMG- multi-arm Adaptive and Combinatorial Trial) aims to implement a highly innovative clinical trial design of combinatorial arms for patients with diffuse midline gliomas (DMGs) at all disease stages that is adaptive to pre-clinical data generated using the DMG-axon assay. The trial is designed to rapidly identify and validate promising drugs for clinical use, and ii) predict biomarkers for promising drugs. METHODS: In vitro (n=15) and in vivo (n=8) models of DMGs across seven institutions were used to assess sensitivity to drug treatments with single drugs OFC201, OFC206, panobinostat, Val-083, and TAK228. In vivo pharmacokinetic assays using clinically relevant dosing of OFC201, OFC206, and panobinostat were performed. Predictive biomarkers for OFC201 and OFC206 were identified using extensive molecular assays including CRISP, RNAseq, ELISA, FACS, and IHC. RESULTS: Inhibitory concentrations (IC50) were established and validated across participating sites. In vivo validation of single and combination drug assays confirmed drug efficacy as increased survival for: OFC201 (p=0.01), OFC206 (p=0.01), OFC201+OFC206 (p=0.02), and OFC201+panobinostat (p=0.01). Marzomib showed toxicity in murine ezbrafish PDX models. Murine pharmacokinetic analysis showed peak brain levels of OFC201 and OFC206 above pre-clinical IC50. Molecular testing and analyses of existing drug screen across 537 cancer cell lines identified single and combination drug efficacies that correlated with the goals of the trial. CONCLUSION: This study was limited by toxicity and poor blood brain barrier penetration. In conclusion, we show that there is a suggestion of efficacy in this approach to treatment for patients, indicating a need to expand on this treatment approach with individualized medicine.

DIPG-68. ALPHA-THALASSEMIA X-LINKED MENTAL RETARDATION PROTEIN (ATRX) LOSS-OF-FUNCTION IN A MOUSE MODEL OF DIFFUSE INTRINSIC PONTINE GliOMA

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Diffuse Intrinsic Pontine Glioma (DIPG) is a rare pediatric brain tumor for which no cure or effective treatments exist. Previous discoveries have revealed that DIPG harbors distinct genetic alterations, when compared with adult high-grade glioma (HGG) or even with non-DIPG pediatric HGGs. ATRX alterations are found in 9% of clinical cases of DIPG, and significantly overlaps with H3.3K27M mutation and p53 loss, the two most common genetic changes in DIPG, found in 80% and 77% clinical cases, respectively. Here we developed genetically engineered mouse model of brainstem glioma using the Rcas2-taAtrx::Pgrmc1 mice, targeting Pgrmc1, H3.3K27M, p53 loss, ATRX loss-of-function and Nestin expression brainstem progenitor cells of the neonatal mouse. Specifically, we used Nestin-Tva-a; p53 floxed; ATRX heterozygous female and Nestin-Tva-a; p53 floxed; ATRX floxed male to generate the Mdx, M1 and M2 models, respectively. Median survival of the three groups are 65 days, 88 days and 51 days, respectively. Also, ATRX null mice is lower in tumor incidence (44%). Compared with ATRX WT (80%). We evaluated the pathological features of DIPG with or without ATRX alteration. RNA-seq was performed to identify differentially expressed genes between ATRX WT and loss-of-function. In conclusion, this study generated the first genetically modified mouse model studying DIPG in vivo and focuses on the role of ATRX loss-of-function in DIPG may slow down tumorigenesis and decrease tumor incidence.