Preclinical data indicates that veliparib crosses the blood-brain-barrier and enhances the efficacy of radiotherapy and temozolomide in IDH mutant and wild-type HGG models. ACNS1721 was a single-arm, non-randomized phase 2 clinical trial designed to determine whether treatment with veliparib and radiotherapy, followed by the poly (ADP-ribose) polymerase (PARP) inhibitor veliparib and temozolomide, improves progression-free survival (PFS) in pediatric patients with newly diagnosed HGG without H3 K27M or BRAF mutations compared to patient level data from historical cohorts with closely matching clinical and molecular features. METHODS: Following surgical resection, newly diagnosed children with non-metastatic HGG were screened by rapid central pathology review and molecular testing. Eligible patients without somatic H3 K27M or BRAF mutations were enrolled on Stratum 1 (IDH wild-type) or Stratum 2 (IDH mutant). Protocol radiochemotherapy consisted of involved field radiotherapy with concurrent veliparib at 65 mg/m^2 twice daily. Adjuvant chemotherapy consisted of up to 10 cycles of veliparib 25 mg/m^2 twice daily and temozolomide 135 mg/m^2 once daily for 5 days every 4 weeks. RESULTS: Both strata were closed to accrual for futility after planned interim analyses. Among the 23 eligible patients who enrolled on Stratum 1 and received protocol therapy, the 1-year progression-free survival (PFS) was 0.29 (SE = 0.09) and 1-year overall survival (OS) was 0.67 (SE = 0.10). Among the 14 eligible patients who enrolled on Stratum 2 and received protocol therapy, the 1-year PFS was 0.57 (SE = 0.15) and 1-year OS was 0.90 (SE = 0.09). **CONCLUSION:** Rapid central pathology review and molecular testing was feasible. The protocol therapy was well tolerated but failed to improve outcome compared to clinically and molecularly matched historical control cohorts.

HGG-08. LORLATINIB FOR THE TREATMENT OF ALK FUSION POSITIVE INFANT HIGH GRADE GLIOMA

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BACKGROUND: High grade gliomas (HGG) are very rare in the infant age group with approximately 800 cases diagnosed in the USA and Europe each year. Histologically, HGG in infants resemble HGG in older children and adults but have distinct molecular features like ALK, NTRK, MET and ROS1 fusions. HGG in infants have superior outcomes compared to older age groups (5-year overall survival >50%) when treated with a radiation sparing regimen. Here we present the unique treatment course for an infant with ALK fusion positive HGG, including molecularly targeted therapy. CASE DESCRIPTION: A 3-month-old African-American female presented with acute onset vomiting, right facial droop and focal seizures. MRI of the brain revealed a right frontal intraparenchymal mass. Upfront gross total resection (GTR) was performed and histologic diagnosis of epithelioid glioblastoma was made. The molecular analysis of the tumor showed ZNF397-ALK fusion. The patient was treated with a radiation sparing regimen consisting of Carboplatin 8 mg/kg x 2 days and Etoposide 3 mg/kg x 3 days for 6 cycles. The patient tolerated the chemotherapy and had no evidence of disease recurrence at the completion of chemotherapy. However, 8 months after completion of therapy, she had a localized relapse and underwent a second GTR. Repeat molecular analysis confirmed the presence of ZNF 397-ALK fusion. She was started on Lorlatinib at 95 mg/m2/day once a day. She continued on the medication for 15 months and had no evidence of disease at the end of 15 months. During the course of her treatment, she had excessive weight gain (CTCAE grade-3) despite dose reduction. CONCLUSION: Infant high grade gliomas have a high prevalence of gene fusions including ALK fusions. This case shows that these fusions may be amenable to molecularly targeted treatments and should be studied in prospective clinical trials.

HGG-09. MICRORNAS EXPRESSION PROFILE IN MENINGIOMA 1 (MN1) GENE ALTERED ASTROBLASTOMA

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Astroblastoma is a rare glial neoplasm arising more frequently in young, predominantly female, patients and with unclear clinical behavior and outcome. The diagnostic molecular alteration is the rearrangement of meningioma 1 (MN1) gene.However, little is known about the specific mechanism of tumor development driven by such genetic change. microRNAs (miRNAs) are important gene expression regulators with strong implications in several biological processes. In this study we investigated the microRNAs' expression and regulation in MN1 altered neoplasms. We collected a cohort of 14 formalin-fixed, paraffin-embedded (FFPE) tumor samples histologically defined classified as astroblastoma. The DNA methylation analysis showed that only 8 cases harbored the MN1 rearrangement characteristic of astroblastoma. The 8 MN1 altered tumors were analyzed for their expression pattern of miRNAs by Nanostring technology. Thirty-nine deregulated miRNAs were found in the 8 astroblastomas compared to normal brain tissue. In order to understand the underlying mechanisms of the miRNAs aberrant expression, we first investigated the methylation status of themicroRNA promoters. Thirty-two out 39 deregulated miRNA resulted epigenetically regulated. with methylation status coherent with microRNA expression in 14/32 miRNAs.. Secondly, we investigated the hypothesis of a genomic alteration as a reason for the abnormal expression of the remaining 18/32 deregulated miRNAs by analyzing the Copy Number Variation (CNV) of tumor samples. but no alteration was found on miRNAs chromosome loci. Finally, we identified validated targets of the 32 deregulated miRNAs and uncovered biological processes putatively correlated to miRNA target genes, clinically and pathologically relevant in MN1-altered astroblastomas. Our findings shed light on the biology of this rare disease with potential implications on prognostic markers and therapy.

HGG-10. EFFICACY OF CONVECTION-ENHANCED DELIVERY OF GB-13 (IL13.E13K-PE4E) IN AN ORTHOTOPIC XENOGRAFT MODEL OF HIGH-GRADE GLIOMA IS PREDICATED ON IL-13RA2 EXPRESSION.

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High-grade gliomas (HGG) encompass a large proportion of malignant tumors within the central nervous system. Despite advances in our understanding of underlying disease mechanisms, the prognosis remains dismal and efficacious therapies are lacking. As such, there is a dire, unmet, gap in clinical practice for treating this devastating disease. Here, we performed convection-enhanced delivery (CED) of GB-13 (also known as IL13.E13K-PE4E), a tumor-specific immunotoxin, into the mouse brain in an effort to assess safety and efficacy. Fifty-five nude mice were inoculated with cells from 3 distinct patient-derived HGG cell lines (low, medium and high IL-13Rα2 expression). After tumor size reached a pre-determined threshold, mice underwent stereotactic cannula placement into the tumor followed by a single 40-min ramped infusion (rate 0.2-0.8 ul/min) of GB-13 (volume of infusion 20 ul) at concentrations ranging from 5 to 50 ug/ml. Tumor progression was monitored semiweekly and animals were euthanized at the indication of progressive neurologic deficit. All animals tolerated the infusions without exhibiting any neurological changes. GB-13 decreased tumor burden and prolonged survival in a manner strongly associated with IL-13Rα2 expression. While no survival benefit was observed in animals harboring IL-13Rα2-low expressing HGG, IL-13Rα2-medium and -high animals lived significantly longer after GB-13 infusion than vehicle-treated animals (median survival prolongation >25 days). Postmortem examination of the brains revealed no morphological changes beyond the site of the cannula tract. While GB-13 decreased cell proliferation and increased the number of apoptotic cells, neuronal cell density in ipsilateral brain regions was retained and no monocyte infiltrate was evidenced following GB-13 exposure. These findings indicate that a single therapeutic infusion of GB-13 administered by CED is well tolerated and underscore the potential of IL-13Rα2-targeted therapies in a subset of HGG with increased IL-13Rα2 expression.

HGG-11. CLINICAL CHARACTERISTICS AND CLINICAL EVOLUTION OF A LARGE COHORT OF PEDIATRIC PATIENTS WITH PRIMARY CENTRAL NERVOUS SYSTEM (CNS) TUMORS AND TROPOMYOSIN RECEPTOR KINASE (TRK) FUSION.

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BACKGROUND: TRK fusions are detected in less than 3% of CNS tumors. Given their rarity, there are limited data on the clinical course of these patients. METHODS: We contacted 166 oncology centers worldwide to retrieve data on patients with TRK fusion-driven CNS tumors. Data extracted included demographics, histopathology, NTRK gene fusion, treatment modalities and outcomes. Patients less than 18 years of age at diagnosis were included in this analysis. RESULTS: Seventy-three pediatric patients with TRK fusion-driven primary CNS tumors were identified. Median age at diagnosis was 2.4 years (range 0.0–17.8) and 60.2 % were male. NTRK2 gene fusions were found in 37 patients (50.7%), NTRK1 and NTRK3 aberrations were detected in 19 (26.0%) and 17 (23.3%), respectively. Tumor types included 38 high-grade gliomas (HGG; 52.1%), 20 low-grade gliomas (LGG; 27.4%), 4 embryonal tumors (5.5%) and 11 others (15.1%). Median follow-up was 46.5 months (range 3-226). During the course of their disease, a total of 62 (84.9%) patients underwent surgery with a treatment intent, 50 (68.5%) patients received chemotherapy, 35 (47.9%) patients received radiation therapy, while 34 (46.6%) patients received NTRK inhibitors (3 as first line treatment). Twenty-four (32.9%) had no progression including 9 LGG (45%) and 9 HGG (23.6%). At last follow-up, only one (5.6%-18 evaluable) patient with LGG died compared to 11 with HGG (35.5%-31 evaluable). For LGG the median progression-free survival (PFS) after the first line of treatment was 17 months (95% CI: 0.0-35.5) and median overall survival (OS) was not reached. For patients with HGG the median PFS was 30 months (95% CI: 11.9-48.1) and median OS was 182 months (95% CI 20.2-343.8). CONCLUSIONS: We report the largest cohort of pediatric patients with TRK fusion-driven primary CNS tumors. These results will help us to better understand clinical evolution and compare outcomes with ongoing clinical trials.

HGG-12. RAPID PTEFB-DEPENDENT TRANSCRIPTIONAL REORGANIZATION UNDERPINS THE GLIOMA ADAPTIVE RESPONSE TO RADIOTHERAPY

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BACKGROUND: Dynamic regulation of gene expression is fundamental for cellular adaptation to exogenous stressors. PTEFb-mediated promoter proximal pause-release of Pol II is a conserved regulatory mechanism for synchronous transcriptional induction best described in response to heat shock, but this pro-survival role has not been examined in the applied context of cancer therapy. DESIGN/METHOD: In order to examine the dynamics of chromatin reorganization following radiotherapy, we performed a combination of ChIP-, ATAC-, and RNA-seq in model systems of diffuse intrinsic pontine glioma (DIPG) and other pediatric high-grade gliomas (pHGG) following IR exposure. We interrogated IR-induced gene expression in the presence or absence of PTEFb blockade, including both mechanistic and functional consequences of concurrent inhibition or genetic depletion. We utilized culture models with live cell imaging to assess the therapeutic synergy of PTEFb inhibition with IR, as well as the therapeutic index of this intervention relative to normal controls. Finally, we employed orthotopic models of pHGG treated with conformal radiotherapy and CNS-penetrant PTEFb inhibitors in order to assess tolerability and anti-tumor effect in vivo. RESULTS: Rapid genome-wide redistribution of active chromatin features and PTEFb facilitates Pol II pause-release to drive nascent transcriptional induction within hours of exposure to therapeutic ionizing radiation. Concurrent inhibition of PTEFb imparts a transcription elongation defect, abrogating canonical adaptive programs such as DNA damage repair and cell cycle regulation. This combination demonstrates a potent, synergistic therapeutic potential agnostic of glioma subtype, leading to a marked induction of tumor cell apoptosis and prolongation of xenograft survival. CONCLUSION: These studies reveal a central role for PTEFb underpinning the early adaptive response to radiotherapy, opening new avenues for combinatorial treatment in these lethal malignancies.

HGG-13. COMBINED CDK INHIBITION AND ARGININE-DEPRIVATION AS TARGETED THERAPY FOR ARGININE-AUXOTROPHIC GLIOBLASTOMA MULTIFORME CELLS

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INTRODUCTION/BACKGROUND: Glioblastoma multiforme show constitutive activation of cyclin-dependent kinases (CDKs) or arginine auxotrophy. This renders tumor cells vulnerable towards arginine-depleting substances, such as arginine deiminase from Streptococcus pyogenes (SpyADI). Previously, we confirmed the susceptibility of patient-derived GBM cells towards administration of SpyADI as well as CDK inhibitors (CDKis). To improve effects, we applied a sequential (SEQ) CDKi/SpyADI approach to examine mechanistic insights and drug susceptibility. MATERIALS AND METHODS: Three arginine-auxotrophic patient-derived GBM lines with different molecular characteristics were cultured in 2D and 3D (spheres and glioma stem-like cells (GSC)) and effects of this combined CDKi/SpyADI approach were analyzed. This included viability staining via Calcein AM in 2D and 3D-Glo in 3D culture and cell death analysis via flow cytometry. Therapy-induced morphological changes were identified with transmission electron microscopy (TEM). Besides, 3D-invasiveness, cellular stress, and DNA damage responses were measured. RESULTS: All SEQ-CDKi/SpyADI combinations yielded synergistic antitumoral effects, characterized by impaired cell proliferation, invasiveness, and viability. Notably, this SEQ-CDKi/SpyADI approach was most effective in 3D models. Mitochondrial impairment was demonstrated by increasing mitochondrial