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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