glioblastoma and downregulated the NFκB pathway. Because this pathway is overexpressed in DIPG and may play a role in DIPG cell growth and survival, we hypothesized that RG2833 would kill DIPG cells. Treatment of DIPG cell lines with RG2833 as a single agent suppresses cell proliferation in the 5–10μM range (MTS assay for HSJD007 p=0.0004 10μM vs DMSO, JHH-DIPG1 p=0.001 10μM vs DMSO, SF-7761 p=0.04 10μM vs DMSO, SU-DIPG13 p=0.01 10μM vs DMSO by *t-test*). RG2833 induces apoptosis by 48 hours as measured by Western blot for cPARP and cleaved caspase 3 immunofluorescence (HSJD007 p<0.003 8μM vs DMSO, JHH-DIPG1 p=0.0026 10μM vs DMSO by *t-test*). RG2833 also slows cell proliferation as measured by Western blot for pRb and immunofluorescence for BrdU (HSJD007 p=0.008 8μM vs DMSO, JHH-DIPG1 p=0.0002 10μM vs DMSO by *t-test*). Western blot confirmed a dose-dependent increase in histone 3 acetylation with RG2833 treatment at 5 hours. We detected increased acetylated p65 and decreased expression of the NFκB regulated pro-survival genes BCL2, BCL-xL, and XIAP with RG2833 treatment. Together, this data shows that HDAC inhibitor RG2833 may be a promising therapeutic candidate for DIPG via downregulation of the NFκB pathway.

DIPG-72. LONG-TERM SURVIVAL OF A CLASSIC DIFFUSE INTRINSIC PONTINE GLIOMA TREATED WITH NIMOTUZUMAB

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BACKGROUND: Long-term survival in diffuse intrinsic pontine glioma is rare, and typically associated with atypical imaging and/or atypical clinical course. Although most patients harbor hotspot mutations in H3.1/3-K27M, a proportion of patients have alternate mutations, despite a typical clinicoradiological course. Herein we describe a long-term survivor with a classical presentation, treated with nimotuzumab, highlighting the challenges associated with such cases. CASE REPORT: A 5 year old male, diagnose in 2012 with a 10 day history multiple cranial neuropathies and a right hemiparesis. Cranial MRI revealed a poorly delimited diffuse pontine tumor and secondary hydrocephalus. Tumor biopsy was not performed due to the classic clinical presentation, and he received 54Gy/30 of radiation plus concomitant weekly nimotuzumab 150mg/m2. Initial tumor dimensions were 43x31x28mm. Nimotuzumab 150mg/m2 was continued every 2 weeks. Image assessment at week 12 of treatment revealed 16.9% volume increase, 4 weeks after radiotherapy completion. Nevertheless, subsequent neuroimaging at 24th, 36th, 60th, 96th and 108th weeks of nimotuzumab therapy showed a sustained and progressive tumor cytoreduction of 47.5%, 59%, 62.2%, 63.8% and 67%, respectively, when compared with post-radiotherapy dimensions. Currently, the patient is 13y old, good school performance, no neurologic disabilities. The last MRI at 394 weeks of nimotuzumab revealed dimensions of 21x19x14mm which corresponds to 70% of reduction compared with initial volume. CONCLUSIONS: Our case of progressive cytoreduction over two years of a classic DIPG, diagnosed in the era prior to the discovery of the K27M mutation, highlights the challenges associated with long-term survival of this devastating entity.

DIPG-73. SENESCENCE ASSOCIATED SECRETORY PHENOTYPE AS A MECHANISM OF RESISTANCE AND THERAPEUTIC VULNERABILITY IN BMI1 INHIBITOR TREATED DIPG

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BACKGROUND: Diffuse intrinsic pontine gliomas (DIPGs) driven by mutations in the histone 3 (H3) gene (H3K27M) are aggressive pediatric brain tumors for which there is no curative therapy. METHODS: To identify novel therapeutic targets we performed a high throughput drug screen combined with an epigenetically targeted RNAi screen using H3K27M and H3.3 WT DIPG cells. RESULTS: Chemical and genetic depletion of BMI1 *in vitro* resulted in inhibition of clonogenicity and cell self-renewal consistent with previous studies. We show for the first time that clinically relevant BMI1 inhibitors attenuates growth of orthotopic DIPG xenografts as measured by MRI and prolong survival *in vivo*. We found that BMI1 inhibition drives phenotypic cellular senescence and that the senescent cells were able reactivate to form new neurospheres *in vitro* and tumor growth *in vivo*. RNA-seq, ChIP-Seq and immuno-proteomic analysis revealed that the senescent cells induced the expression of the Senescence Associated Secretory Phenotype (SASP) cytokines by increasing occupancy of activated histone marks at SASP factor promoters. The SASP results in increased expression of anti-apoptotic BH3 proteins including BCLxl, and BCL2. Treatment of the PTC028 treated senescent DIPG cells with BH3 mimetics induces apoptosis and clears the senescent cells. Combining BH3 mimetics with BMI1 inhibition attenuates tumor growth *in vivo* synergistically and significantly prolongs survival of DIPG bearing mice compared to BMI1 inhibition alone. CONCLUSION: These data inform the current trial of BMI1 inhibition as a monotherapy and predict the need for adding BH3 mimetics to achieve efficacy.

DIPG-74. RE-IRRADIATION OF DIPG: DATA FROM THE INTERNATIONAL DIPG REGISTRY

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PURPOSE: To review data from DIPG Registry patients recorded to have received a second course of radiation therapy (rRT). METHODS: The International DIPG Registry was searched for patients with DIPG who were treated with a known dose of rRT. Doses of rRT, timing from initial diagnosis and primary radiation therapy (pRT), radiographic response to rRT and survival from diagnosis (OS) were evaluated. RESULTS: Sixty (11.2%) of 535 Registry patients underwent rRT; dose was provided for 44 patients. Median (range) data from those 44 revealed that rRT was given at 12 (2–65) months from initial diagnosis of DIPG and at 9.6 (1–61) months from completion of pRT at a dose of 26.7 (1.8–74) Gy. After completion of rRT, MRI showed response, progression, stable disease or was not available in 19, 8, 3 and 14 patients, respectively. Median PFS and OS were 11 and 18.1 months, respectively. 475 Registry patients did not undergo rRT; their ages, duration of symptoms, and primary treatment with or without chemotherapy were not significantly different from the rRT cohort. Median PFS and OS for the non-rRT patients were 6.9 and 10 months, respectively. rRT patients were more likely to have had radiographic evidence of tumor necrosis at diagnosis than non-rRT patients. CONCLUSIONS: Administration of rRT to patients with DIPG has been inconsistent with respect to timing and dose. Toxicity,