CED. METHODS: CED was performed between 4-14 weeks post radiation therapy. Using a 3 + 3 design, ^{124}I-omburtamab was escalated from 0.25-10.0 mCi and infusion volumes (Vi) from 250-10,000 µl with serial ^{124}I PET/CT performed up to ~1 week post-administration. Toxicities were assessed for 30 days. Dose escalation safety was evaluated. Survival was calculated using Kaplan-Meier statistics. RESULTS: 46 children were treated and evaluable for toxicity and survival;4 patients received partial doses and were evaluable for toxicity only. Three patients experienced dose limiting toxicities. Eleven patients had transient treatment related grade 3 toxicities with no grade 4 or 5 toxicities. Grade 3 nervous system toxicities included: muscular weakness(n=8), dysarthria(n=4), ataxia(n=3), dysphagia(n=3), and gait disturbance(n=1). Lesion absorbed doses ranged from 1,000-1,500cGy/mCi, with lesion-to-whole body radiation absorbed-dose ratios of ~900. A dose of 8mCi and infusion volume of 8,000 µl is safe and may provide a distribution volume up to 20cm^3. Median survival was 15.3 months (n =46, 95% CI 12.7, 17.3). Survival rate estimates (95% CI) at 1, 2, 3 and 5 years were 0.67 (0.55;0.82); 0.18 (0.09;0.35); 0.10 (0.04;0.26); and 0.05 (0.01;0.20). Four patients survived >3 years; two remain alive (61+ and 106+ months);two have died (44 and 53 month) with distant CNS disease and one with extra-CNS metastasis. **CONCLUSION:** Administration of escalating doses and volumes of ^{124}I-omburtamab via CED was a viable option for this patient subgroup. The median overall survival was increased 3-4 months compared to historical controls. Anecdotal long-term survival if validated with a planned phase 2 trial would support the concept of whole neuroaxis treatment in combination with CED in a subset of DIPG patients.

DIPG-54. P53 PATHWAY REACTIVATION AS A THERAPEUTIC STRATEGY IN DIFFUSE INTRINSIC PONTINE GLIOMA

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TP53 is the most frequently mutated tumor suppressor with somatic alterations found in approximately 50% of all human cancers. In the remaining TP53 wild-type (WT) tumors, functional inactivation of the p53 pathway may be achieved through a variety of other mechanisms, including gene deletion, epigenetic silencing, and/or alterations in prominent negative regulators, including MDM2/MDM4 and PPM1D. These alterations block p53 activity and lead to uncontrolled cell proliferation and oncogenesis in a majority of cancers, including the highly aggressive, universally fatal glial cell tumors of childhood, known as Diffuse Intrinsic Pontine Gliomas (DIPGs). DIPGs are inoperable due to their location within the brainstem. Available treatment options, including radiotherapy, have had a palliative effect at best, with almost all children succumbing to the disease within 18 months of diagnosis. Recent advances have led to an improved understanding of the biological underpinnings of this disease and identification of recurrent genetic alterations that represent potential therapeutic targets for these patients. Prominent among these targets in DIPGs with WT p53 status (50%) are MDM2/4 and PPM1D, whose suppression lead to p53 reactivation specifically in the WT p53 context. We have undertaken a combination of approaches to better understand the therapeutic potential of MDM2 and PPM1D inhibition in DIPG, characterizing the genomic, transcriptomic, and cell-state changes that drive resistance, and identifying novel vulnerabilities that can be exploited with combination therapies towards a cure.

DIPG-55. INCREASING THE DRUG-TUMOR RESONANCE TIME IN DMG MURINE MODELS SIGNIFICANTLY EXTENDS SURVIVAL

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H3K27-altered diffuse midline glioma (DMG) is a uniformly lethal CNS cancer that predominately occurs in children. In the last decade, while studies revealing the molecular underpinnings of the disease have paved the way for novel therapeutic strategies, this tumor remains a death sentence. Our lab and others have identified numerous drugs of high interest for treating this devasting disease, however, every trial has failed to show benefit. Is our failure to translate these laboratory findings due to the fact we have not found the right drugs or treatment regimens yet? Or is this a failure to get the drugs to the tumor? Or is this simply a very bad disease to treat? The answer is likely multifactorial. Our lab, in collaboration with others, have strong data to show that simply getting drugs to the tumor will not result in a positive benefit. Most drugs are rapidly cleared from their target space. Utilizing techniques that increase the drug-tumor resonance time is necessary to translate our basic science findings to our patients. Picking the right drug and the delivery mechanism is not enough for a positive effect. Here, we assessed the efficacy of a previously identified inhibitor, alisertib, delivered by short-term convection-enhanced delivery or a continuous osmotic pump and found that continuous, direct delivery results in a significant increase in survival (p = 0.0002). Furthermore, long-term survivors showed a decreased tumor burden and on-target drug effects. These data support that translation into patients must consider three factors: 1) selection of a potent therapy, 2) selection of the proper delivery method for that therapy, 3) modulation to ensure that the therapy remains in the targeted tissue long enough for desired effect. Keeping these basic tenets at the forefront of development may finally lead to a more effective treatment strategy for this devastating disease

DIPG-56. DEVELOPMENT AND APPLICATION OF A NOVEL ANTIBODY AGAINST CD99 AS A THERAPEUTIC STRATEGY IN DIFFUSE MIDLINE GLIOMA

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BACKGROUND: There is an unmet need to identify novel targeted therapies for Diffuse Midline glioma (DMG) which is currently a refractory disease. Recently, we identified high expression of a cell surface antigen, CD99 in H3K27M-mutant expressing DMGs compared to other normal brain counterparts. We developed a novel chimeric CD99 antibody and tested the anti-tumor efficacy of this antibody in vitro and in vivo. **METHOD:** Bio-legend cell-surface screening was performed in H3K27M-mutant and WT DMG cells. Functional role of CD99 was studied using CD99 proficient and depleted tumors. Designed and synthesized CD99 antibody with a new binding sequence on a human IgG scaffold and performed cell toxicity and growth-inhibitory studies using DMG tumor and normal cells. We also performed these studies in combination with radiation. Multiple patient-derived orthotopic DMG xenograft models was used to test the antibody efficacy. Different antibody delivery routes, that are clinically relevant were investigated. RESULTS: CD99 expression is transcriptionally regulated by H3K27M and is enriched on the cell surface of K27M tumors compared to WT DMG tumors. Our new CD99 antibody (10D1 clone) significantly reduced DIPG tumor cell proliferation in vitro. Intravenous infusion of this antibody in DIPG tumor bearing mice showed complete clearance of tumor that prolonged animal survival suggesting the enhanced anti-tumor efficacy of 10D1-CD99 and importantly, its ability in crossing the blood-brain-barrier and reaching the pons target site. Loco-regional administration of 10D1 showed similar anti-tumor effects even at much reduced antibody concentrations while toxicity to CD99-expressing T cells was minimum. Radiation increased CD99 expression and enhanced the cytotoxic effect of 10D1-CD99. **CONCLUSION:** We have developed a novel CNS penetrant CD99 antibody that is an attractive therapeutic strategy in treating DMG. 10D1 is currently in development as a therapeutic.

DIPG-57. A SYSTEMS BIOLOGY APPROACH TO DEFINING AND TARGETING MASTER REGULATOR DEPENDENCIES FROM BULK AND SINGLE-CELL RNA-SEQ IN DIFFUSE MIDLINE GLIOMA (DMG)

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Diffuse midline glioma (DMG) are fatal pediatric brain tumors with no effective systemic therapies. Molecular profiling demonstrates epigenetic dysregulation and heterogeneity, and novel approaches are needed to identify promising drugs and drug combinations. We used network-based computational analysis of RNA-seq to discover Master Regulator (MR) proteins that represent targetable, mechanistic determinants of distinct DMG cell states. We reverse-engineered the first DMG-specific regulatory network from 122 publicly available DMG RNA-seq profiles with ARACNe. Using this network, we measured sample-specific protein activity based on differential expression of their targets via VIPER. Activity-based clustering identified two clusters showing a trend in survival differences (>1 year, by $\chi 2$). The most activated MRs (i.e., TOP2A, CENPF, BUB1B, FOXM1, GTSE1, MKI67, E2F8), relative