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DIPG-52. PHASE I CLINICAL TRIAL OF ONC201 IN PEDIATRIC H3 K27M-MUTANT GLIOMA OR NEWLY DIAGNOSED DIPG

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(DIPGs), a pediatric glioma with 2-year survival rate of less than 10%. *ACVR1*mutations frequently coincide with activating *PIK3CA* or *PIK3R1* mutations, indicating a potential cooperative effect of BMP and PI3K signaling in gliomagenesis. We used genetically engineered mice with inducible knock-in of *Acvr1*^{R206H} or *Pik3ca*^{E545K} alleles, such that cre-mediated recombination resulted in expression of the gain of function mutated genes from their endogenous promoters at physiological levels. Cre-mediated deletion in *GFAP-CreER;Pik3caE545K/+;p53cKO* mice (*Pik3ca;p53*) mediated *Trp53* deletion and expression of *Pik3caE545K* in glial progenitors, and spontaneously induced high-grade glioma (HGG) in mice with complete penetrance. Heterozygous knock-in of the *Acvr1R206H* allele accelerated tumorigenesis and impaired survival in *Pik3ca;p53* mice (*Acvr1;Pik3ca;p53*). Transcriptomic analysis of *Acvr1;Pik3ca;p53* tumors compared to *Pik3ca;p53* littermate controls, as in patient-derived tumors, revealed broad molecular signatures associated with cell fate commitment and chromosome maintenance. Pharmacologic inhibition of ACVR1 was sufficient to impair growth in human patient-derived DIPG cell lines. Together, our studies show that ACVR1 activation promotes tumor growth in spontaneous mouse HGG and patient-derived DIPG cells, suggesting that ACVR1 inhibition may produce a clinically significant therapeutic effect in DIPG.

DIPG-52. PHASE I CLINICAL TRIAL OF ONC201 IN PEDIATRIC H3 K27M-MUTANT GLIOMA OR NEWLY DIAGNOSED DIPG

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H3 K27M-mutant gliomas often manifest as midline gliomas, have a dismal prognosis, and have no effective treatments. ONC201 efficacy has been shown in high-grade glioma preclinical models and durable responses with single agent ONC201 have been reported in adults with recurrent H3 K27M-mutant gliomas. These observations led to a Phase I pediatric clinical trial of ONC201 dosed by body weight. This multicenter, open-label, 3 + 3 dose-escalation and dose-expansion clinical trial (NCT03416530) for H3 K27M-mutant glioma or non-biopsied DIPG has 6 arms: arms A and E determine the RP2D in pediatric post-radiation (recurrent or not-recurrent) H3 K27M-mutant glioma patients with ONC201 administered as an oral capsule as well as a liquid formulation, respectively. Both arms have completed accrual. The study is currently enrolling newly diagnosed DIPG patients to determine the RP2D for ONC201 in combination with radiation (arm B). Dedicated assessment of intratumoral ONC201 concentrations in midline gliomas patients (arm C) and the effects of ONC201 in H3K27M DNA levels in circulating CSF (arm D) are currently enrolling patients. ONC201 as a single agent in patients with progressive H3K27M mutant tumors following irradiation (excluding DIPG/spinal cord tumors) was recently opened (arm F). Once the RP2D is confirmed, there is a dose-expansion cohort to confirm the safety, radiographic efficacy and survival with ONC201. The primary endpoints of arms A, B, and E have been established with the RP2D of 625mg scaled by body weight as a capsule or liquid formulation administered alone or in combination with radiation without incidence of dose-limiting toxicity.

DIPG-53. CHARACTERIZING THE ROLE OF PPM1D MUTATIONS IN THE PATHOGENESIS OF DIFFUSE INTRINSIC PONTINE GLIOMAS (DIPGS)

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INTRODUCTION: We have previously found that up to 15% of all DIPGs harbor mutations in *PPM1D*, resulting in the expression of an activated and truncated *PPM1D (PPM1Dtr)*. Here we evaluate the mechanisms through which *PPM1Dtr* enhances glioma formation and identify its associated therapeutic vulnerabilities. METHODS: We have developed multiple in vitro and in vivo models of *PPM1D*-mutant DIPGs and applied quantitative proteomic and functional genomic approaches to identify pathways altered by *PPM1Dtr* and associated dependencies. RESULTS: *PPM1D* mutations are clonal events that are anti-correlated to *TP53* mutations. We find ectopic expression of *PPM1Dtr* to be sufficient to enhance glioma formation and to be necessary in *PPM1D*-mutant DIPG cells. In addition, endogenous truncation of *PPM1D* is sufficient to enhance glioma formation in the presence of mutant *H3F3A* and *PDGFRA*. *PPM1Dtr* overexpression attenuates g-H2AX formation and suppresses apoptosis and cell-cycle arrest in response to radiation treatment. Deep scale phosphoproteomics analyses reveal DNA-damage and cell cycle pathways to be most significantly associated with *PPM1Dtr*. Furthermore, preliminary analysis of genome-wide loss-of-function CRISPR/Cas9 screens in isogenic GFP and *PPM1Dtr* overexpressing mouse neural stem cells reveal differential dependency on DNA-damage response genes in the *PPM1Dtr* overexpressing cells. Consistent with *PPM1D*'s role in stabilizing *MDM2*, *PPM1D*-mutant DIPG models are sensitive to a panel of *MDM2* inhibitors (Nutlin-3a, RG7388, and AMG232). CONCLUSION: Our study shows that *PPM1Dtr* is both an oncogene and a dependency in *PPM1D*- mutant DIPG, and there are novel therapeutic vulnerabilities associated with PPM1D that may be exploited.

DIPG-54. A NON-INVASIVE PROGNOSTIC CIRCULATING MIRNAS SIGNATURE IN DIFFUSE INTRINSIC PONTINE GLIOMAS

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Diffuse intrinsic pontine gliomas (DIPG) are the most common brainstem tumors of childhood and represent one of the most challenging paediatric tumours to treat. A non-randomized, open label phase II pilot study was conducted at Fondazione IRCCS Istituto Nazionale Tumori (Milan) to assess the efficacy in terms of objective response rate according to the RECIST criteria of combining nimotuzumab and vinorelbine with radiation in newly-diagnosed DIPG. Serum specimens were collected at baseline. microRNA expression profiling was performed using Agilent platform and Human miRNA SureSelect 8x60K containing 2006 miRNAs annotated on miRBase19.0. Primary data analysis yielded a matrix containing 330 detectable miRNA. Association with PFS allowed us to disclose a signature of 10 miRNAs able to stratify high and low risk patients (HR=4.33, 95%CI 1.49–12.54; p=4.27E-05). To test the 10 ct-miRNA model performance, we collected an independent cohort of the same sample size (n=24) and we derived the index values and risk stratification. The distribution of index values covers a range similar to the discovery cohort. Imposing the signature threshold patients were divided in high/low risk and Kaplan-Meier curves confirmed the different PFS time for the two groups with HR=3.5 (95%CI: 1.8–8.01, p-value=0.0002) for the high-risk patients, reaching AUC=0.833. Our signature is a biomarker based on non-invasive procedures for prognosis able to enter into clinical practice. Further validation on multicenter case series is warranted.

DIPG-55. PATTERNS OF CEREBROSPINAL FLUID DIVERSION AND SURVIVAL IN CHILDREN WITH DIFFUSE INTRINSIC PONTINE GLIOMA: A REPORT FROM THE INTERNATIONAL DIPG REGISTRY

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