eral ophthalmologic side effects, including MEK inhibitor-associated retinopathy (MEKAR), also termed central serous-like retinopathy. MEKAR is defined as accumulation of subretinal fluid. It occurs in up to 90% of adults on MEK inhibitors, usually causing minimal to no symptoms, and typically resolving without MEK inhibitor dose adjustment. We report a case of MEKAR in a 15 year old boy with an optic pathway pilocytic astrocytoma with duplication of BRAF (7q34). Baseline ophthalmic exam showed 20/20 vision in his right eye with loss of the temporal hemifield and no light perception vision in the left eye. Nine months into treatment with Selumetinib his ophthalmologic exam and optical coherence tomography (OCT) showed asymptomatic bilateral subretinal fluid. Selumetinib was held for 2 weeks resulting in resolution of the subretinal fluid. Selumetib was resumed at the prior dose and MEKAR recurred 2 weeks later but then permanently resolved 4 weeks later despite remaining on Selumetib. Review of the literature discovered a single publication of 2 pediatric patients with optic pathway glioma who developed MEKAR around 6-7 months after initiating Selumetinib, which resolved after stopping Selumetinib. One patient was symptomatic and despite resolution of symptoms, Selumetinib was not resumed. The other patient was asymptomatic and resumed Selumetib, but redeveloped MEKAR 8 months after restarting Selumetinib. Based on adult experience and the limited pediatric experience outlined above, we recommend pediatric patients with asymptomatic and mild-moderate symptomatic MEKAR undergo close monitoring without Selumetinib dose interruption or modification unless symptoms progress.

LGG-64. A PHASE II STUDY OF PEGYLATED INTERFERON IN CHILDREN WITH RECURRENT OR REFRACTORY AND RADIOGRAPHICALLY OR CLINICALLY PROGRESSIVE JUVENILE PILOCYTIC ASTROCYTOMAS AND OPTIC PATHWAY GLIOMAS (NCT02343224)

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Unresectable Juvenile Pilocytic Astrocytomas (JPA) and Optic Pathway gliomas (OPG) are chronic diseases that can have solid +/- cystic components. We wanted to evaluate the objective response to pegylated interferon Alpha2B in this group of patients in a prospective single arm Phase II clinical trial. Eligibility criteria: age 3 -25 years, patients with neurofibromatosis (NF) were eligible, evidence of measurable disease in MRI, no limitation in the number of prior therapies including chemotherapy and radiation. Exclusion criteria: prior pegylated interferon exposure, less than 2 years from radiation, active autoimmune disease. Subjects enrolled received pegylated interferon 1 mcg/kg/dose SQ weekly, to a max dose of 150mcg/dose in 28 day cycles for up to 2 years. The study design is a Simon two stage design. If no complete or partial responses among the first 9 patients, the study will terminate. Nine subjects enrolled: 4 females, 5 males, median age of 11years, 6 Caucasians, 3 African Americans. Two subjects with NF. Molecular findings KIAA-BRAF fusion (6), V600E mutation (1), CDK2A loss (1). Location: brain (7), brain and spine (2). We enrolled a heavily pre-treated population, patients with prior radiation (1), nine with prior chemotherapy, the average number of regimens 4 (range 2-6). No complete responses or partial responses were seen. Two patients with prolonged stable disease 75+months and 66+ months. At 12 and 24 month EFS 76.2% (95%CI52.1-100%). Median EFS has not been reached. The 12 and 24 months survival estimate 75% (95% CI 50.3-100%), median survival has not been reached. Side effects as expected mostly grade 1-2. No grade 4 event related to pegylated interferon were seen. This is the first report of pegylated interferon in OPG and JPA, two patients with prolonged stable disease suggesting that pegylated interferon can offer potential benefit in this population and additional studies are important.

MEDULLOBLASTOMA

MEDB-01. MANAGEMENT OF THE RISK OF MEDULLOBLASTOMA ASSOCIATED TO FAMILIAL ADENOMATOUS POLYPOSIS AND DYSREGULATED WNT SIGNALOSOME

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APC is the key gene of the familial adenomatous polyposis (FAP). This tumor suppressor gene functions by negatively regulating the β-catenin protein and the majority of APC mutations disrupt the β-catenin degradation complex signalosome leading to the activation of the canonical Wnt pathway. Pathogenic APC mutations were reported in association to medulloblastoma. In this study, we report rare mutations of the APC gene detected in Tunisian families from the governorate of Sfax presenting clinically with various digestive and extra-digestive manifestations. Our goal was to assess the oncogenic risks encountered by our pediatric carriers to offer an accurate genetic counselling, particularly at the neurologic level. Molecular investigation of all members of two families was conducted, using bidirectional sequencing of all 15 exons of the APC gene. A phenotype-genotype correlation was conducted to elucidate the mutational pathophysiological mechanism. Two rare mutations were revealed in our familial study. The first mutation was located at exon 13 and was a missense mutation at codon 1690. The second mutation was a deletion identified at codon 4652 in exon 15. The mutations resulted both in truncated gene products. Clinical manifestations closely depending on the position of the mutation were respectively colic polyposis for the first mutation and soft tissue fibromatous tumors for the second. The localization of the APC mutations allows better targeting of surveillance for clinical manifestations that may be included in FAP. Mutations that remove the Axin-binding sites, as is the case for the first mutation, lead to severe clinical pictures whereas mutations that retain one or two of the Axin binding sites are associated with other features such as desmoid tumors. The risk of the Wnt- medulloblastoma subtype, higher among patients with FAP should be considered with a more awareness of signs and symptoms related to CNS tumors in the FAP context.

MEDB-02. THE IDENTIFICATION AND FUNCTIONAL CHARACTERIZATION OF CIRCULAR RNA CIRC_63706 IN SONIC HEDGEHOG MEDULLOBLASTOMAS

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Circular RNAs (circRNAs) are increasingly recognized as stable and specific biomarkers and therapeutic targets in many cancers, but little is known about their function, subtype specificity, and biomarker potential in medulloblastomas. Medulloblastoma is a central nervous system tumor that predominantly affects children and always requires aggressive therapy. Understanding and identifying novel disease-related molecular mechanisms and pathways are essential for developing optimal and novel therapies. To identify medulloblastoma subgroup-specific circRNAs, we subjected RNA-seq data from 175 clinical medulloblastoma samples representing the four subgroups to a statistical and machine learning (random forest classification) pipeline. Circular RNA circ_63706 expression was specific to the sonic hedgehog (SSH) group, which was confirmed through *in situ* hybridization analysis of clinical tissue samples. Functional characterization of circ_63706 by siRNAs and shRNAs demonstrated that cell proliferation, invasion, and apoptosis are perturbed in circ_63706 cells and inhibited *in vivo* tumor growth. These novel medulloblastoma-specific circular RNAs are emerging as important oncogenes that not only provide valuable mechanistic insights into how medulloblastomas develop but also how they can be used as biomarkers and therapeutic targets. These results pave the way for the specific identification and personalized treatment of different medulloblastoma subgroups.

MEDB-03. MEDULLOBLASTOMA CEREBROSPINAL FLUID REVEALS HYPOXIC INDICATORS (METABOLITES AND LIPIDS) AND CANCER-SPECIFIC RNAS

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Medulloblastoma (MB) is the most common malignant brain tumor in children. There remains an unmet need for diagnostics to sensitively detect the disease, particularly recurrences. Cerebrospinal fluid (CSF) provides a window into the central nervous system, and liquid biopsy of CSF could provide a relatively non-invasive means for disease diagnosis. There has yet to be an integrated analysis of the transcriptomic, metabolomic, and lipidomic changes occurring in the CSF of children with MB. CSF samples from patients with (n=40) or without (n=11; no cancer) MB were subjected

to RNA-sequencing and high-resolution mass spectrometry to identify RNA, metabolite, and lipid profiles. Differentially expressed transcripts, metabolites, and lipids were identified and their biological significance assessed by pathway analysis. Multivariate analysis method DIABLO (R package mixOmics) was used to integrate the molecular changes characterizing the CSF of MB patients. Differentially expressed transcripts, metabolites, and lipids in CSF were discriminatory for the presence of MB but not the exact molecular subtype. One hundred ten genes and ten circular RNAs were differentially expressed in MB CSF compared to normal representing TGF-β signaling, TNF-a signaling via NF-kB, and adipogenesis pathways. Tricarboxylic acid cycle and other metabolites (malate, fumarate, succinate, α-ketoglutarate, hydroxypyruvate, N-acetyl-aspartate) and total triacylglycerols were significantly upregulated in MB CSF compared to normal CSF. Although the transcriptomic, metabolomic, and lipid signatures in CSF to differentiate MB subgroup separation was challenging, we were able to identify a group of omics signatures that could separate cancer from normal CSF. Metabolic and lipidomic profiles both contained indicators of tumor hypoxia. Our approach provides several candidate signatures that deserve further validation, including the novel circular RNA circ_463, and insights into the impact of MB on the CSF microenvironment.

MEDB-04. YOUNG CHILDREN WITH METASTATIC MEDULLOBLASTOMA: FREQUENT REQUIREMENT FOR RADIOTHERAPY IN CHILDREN WITH NON-WNT/NON-SHH MEDULLOBLASTOMA DESPITE HIGHLY INTENSIFIED CHEMOTHERAPY – RESULTS OF THE MET-HIT2000-BIS4 TRIAL

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PURPOSE: To assess outcomes and biological parameters of children younger than 4 years with metastatic medulloblastoma treated within the MET-HIT2000-BIS4 trial or outside the protocol. PATIENTS AND METHODS: 48 trial participants received either carboplatin/etoposide (years 2001 to 2005, n=18) or an intensified Head-Start-based induction (years 2006 to 2011, n=30), both groups with intraventricular methotrexate, followed by high-dose chemotherapy (HDCT) and/or craniospinal radiotherapy (CSI). In an extended cohort, data of 58 additional were grouped with trial participant data. RESULTS: Trial participants (n=48): After intensified induction, both response (26/27 vs. 10/17 eligible patients, p=0.003), and progression-free survival (PFS, 5-year-PFS (5y-PFS): 57% vs 28%, p=0.014) was higher after intensified induction. However, CSI- /progression-free survival (CSIfPFS) was low (5-year CSIfPFS 17%). Biological subtype influenced 5y-CSIfPFS with 3% in non-WNT/non-SHH medulloblastoma vs. 58% in SHH-medulloblastoma (p<0.001), independent of induction regimens. Extended cohort (n=48 on trial and n=58 off trial): Non-WNT/non-SHH medulloblastoma (n=74, all treated in analogy to the MET-HIT2000-BIS4 protocol): Most frequent subtypes were II (5y-PFS 0%, 5y-OS 7%, n=21) and IV (5y-PFS 55%, 5y-OS 57%, n=16). 5y-CSIfPFS was only 8% [n=5]. Among patients in CR (n=13) or PR (n=10), who received HDCT but not CSI in primary therapy, only 5 were CSI-free survivors (CR: n=4/PR: n=1; Subtype III: n=1, Subtype IV: n=2, non-WNT/non-SHH by histology: n=2). SHH-medulloblastoma (n=32, treated with MET-HIT2000-BIS4 [n=16] or HIT2000-BIS4/HIT-SKK chemotherapy [with intrventricular methotrexate, without HDCT; n=16]): 5y-PFS (72%) and 5y-CSIfPFS (69%) did not differ according to therapy or SHH-subgroups. Two therapy-related deaths occurred on MET-HIT2000-BIS4 therapy. Relapses were more frequent after HIT-SKK (p=0.083). CONCLUSIONS: Despite maximally intensified chemotherapy, patients with metastatic non-WNT/non-SHH medulloblastoma almost always require craniospinal radiotherapy to survive their disease. In SHH-activated medulloblastoma, HDCT might better control the disease but careful vigilance of toxicity is important.

MEDB-05. SURVIVAL AND PROGNOSTIC FACTORS IN CHILDHOOD MEDULLOBLASTOMA: A CHINA SINGLE CENTER EXPERIENCE FROM 2006 TO 2015

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OBJECTIVE: Medulloblastoma (MB) is a malignant embryonal tumor that develops especially in childhood, with overall survival (OS) at 5 years of up to 70%. The aim of the study is to explore the clinical profile and