formed against Gnomad3.1 (without cancer samples) using Fisher's exact test with Bonferroni adjustment. We observed 214 P-LP variants involving 190 unique individuals (21.6% of cohort). As expected, the most frequent variants were observed in *NF1, NF2,* and *TP53*(n=40 variants in 21% of individuals). *ATM*, *TSC2* and *CHEK2* variants (n=23) were observed in another 12% of individuals. An increased burden of P-LP variants was observed for 5 of these 6 genes ($p = 1.7x10^{-25}$ to $1.4x10^{-2}$, *CHEK2* $p=5.5x10^{-2}$). We also identified 5 variants in *BRCA2* (3 in high-grade glioma), 7 in REQC helicases (*BLM*, *WRN*, *REQL4*), and 16 variants in Fanconi anemia genes. Overall, cases harbored increased burden in P-LP variants in CPG genes ($p=8.8x^{-18}$) and the subset of DNA repair genes ($p=4.7x10^{-4}$). In conclusion we confirmed the association of variants in established predisposition genes while potentially identifying novel variants and genes associated in CNS tumors.

OMIC-13. THE ROLE OF COPY NUMBER ALTERATIONS IN PREDICTING SURVIVAL AND INFLUENCING TREATMENT OF CHILDHOOD BRAIN TUMORS

Sharon Freshour, Bryan Fisk, Christopher Miller, Obi Griffith, Malachi Griffith, and Joshua Rubin; Washington University School of Medicine, Saint Louis, MO, USA

Brain and central nervous system tumors are the most common form of solid tumor cancers and the second most common cancer overall among children. While many advances have been made in understanding the genomics of childhood brain tumors in recent years, the role of copy number alterations (CNAs) has not been fully characterized. Although the genomes of childhood brain tumor patients are generally considered to be relatively stable diploid genomes, analysis of a subset of pretreatment diagnostic samples from a cohort of 84 deceased patients from Washington University revealed widespread alterations, suggesting CNAs may play a larger role in the progression and prognosis of childhood brain tumors than originally thought. Follow up analysis of the entire cohort, containing a variety of tumor types that had low-pass whole genome sequencing performed, similarly showed evidence of CNAs across samples. 75 out 84 patients showed the presence of CNAs with an average of 16% of the genome being altered per sample and a median of 7%. Preliminary results examining correlations between the percentage of the genome that was copy number altered and event free survival or overall survival indicated that CNA percentage may have some prognostic value. For example, ependymoma samples showed positive correlation between alteration percentage and overall survival, while glioblastoma samples showed negative correlation. To explore copy number alteration in a larger cohort and increase statistical power, similar analyses are being performed using an additional 950 samples from the Pediatric Brain Tumor Atlas curated by The Children's Brain Tumor Network (CBTN) to determine if CNVs and CNV percentage or specific alterations can serve as prognostic markers and whether the biology of this genomic instability could inform therapeutic strategy.

OMIC-14. OPENPBTA: AN OPEN PEDIATRIC BRAIN TUMOR ATLAS

Joshua Shapiro[1], Candace Savonen[1], Chante Bethell[1], Krutika Gaonkar[2], Yuankun Zhu[2], Miguel Brown[2], Nhat Duong[2], Komal Rathi[2], Nighat Noureen[3], Bo Zhang[2], Brian Ennis[2], Stephanie Spielman[4], Bailey Farrow[2], Nicolas Van Kuren[2], Tejaswi Koganti[2], Shrivats Kannan[2], Pichai Raman[2], Daniel Miller[2], Payal Jain[2], Yiran Guo[2], Xiaoyan Huang[2], Adam Kraya[2], Allison Heath[2], Mateusz Koptyra[2], Jessica Wong[2], Jennifer Mason[2], Shannon Robbins[2], Mariarita Santi[2,5], Angela Viaene[2,5], Angela Waanders[6,7], Derek Hanson[8,9], Laura Scolaro[2], Hongbo Xie[2], Siyuan Zheng[3], Cassie Kline[2], Jena Lilly[2], Philip Storm[2], Adam Resnick[2], Jo Lynne Rokita[2], Casey Greene[1,10], and Jaclyn Taroni[1]; [1]Alex's Lemonade Stand Foundation, Philadelphia, PA, USA, [2]Children's Hospital of Philadelphia, Philadelphia, PA, USA, [3]UT Health San Antonio, San Antonio, TX, USA, [4]Rowan University, Glassboro, NJ, USA, [5]University of Pennsylvania, Philadelphia, PA, USA, [6]Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA, [7]Northwestern University Feinberg School of Medicine, Chicago, IL, USA, [8]Hackensack Meridian School of Medicine, Nutley, NJ, USA, [9]Hackensack University Medical Center, Hackensack, NJ, USA, [10]University of Colorado School of Medicine, Aurora, CO, USA

Pediatric brain tumors comprise a heterogeneous molecular and histological landscape that challenges most current precision-medicine approaches. While recent large-scale efforts to molecularly characterize distinct histological entities have dramatically advanced the field's capacity to classify and further define molecular subtypes, developing therapeutic and less toxic molecularly-defined clinical approaches remains a challenge. To define new approaches to meet these challenges and advance scalable, shared biospecimen- and data-resources for pediatric brain tumors, the Children's Brain Tumor Network and Pacific Pediatric Neuro-Oncology Consortium, in partnership with the Alex's Lemonade Stand Foundation Childhood Cancer Data Lab, launched OpenPBTA, a global open science Pediatric Brain Tumor Atlas initiative to comprehensively define the molecular landscape of pediatric brain tumors. The initiative contains multi-modal analyses of research- and clinical-trial based DNA and RNA sequences from nearly 1,000 subjects (with 1,256 tumors) along with their longitudinal clinical data. The OpenPBTA's open science framework for analysis tests the capacity of crowd-sourced collaborative architectures to advance more rapid, iterative and integrated discovery of the underlying mechanisms of disease across pediatric brain and spinal cord tumors. Since the launch of the project, OpenPBTA has collaboratively created reproducible workflows for integrated consensus SNV, CNV, and fusion calling, enabled RNA-Seq-based classification of medulloblastoma subtypes, and more than 25 additional DNA- and RNA-based analyses. The open-science platform and associated datasets and processed results provide a continuously updated, global view of the integrated cross-disease molecular landscape of pediatric brain tumors. Such biospecimen- and clinically-linked scalable data resources provide unprecedented collaborative opportunities for precision-based, personalized therapeutic discovery and drug development with the upcoming further integration of proteomic sample data (N >300) and drug response datasets, additionally diversifying the multimodal discovery potential of crowd-sourced approaches for accelerated impact for children with brain tumors.

RARE TUMORS/OTHER

RARE-01. ASSESSING THE SYMPTOM DIAGNOSTIC INTERVAL FOR CHILDREN WITH CENTRAL NERVOUS SYSTEM TUMOURS

Cameron Crowell[1,2], Bruce Crooks[1,2], Simon Walling[1,2], Kelly Boileau[1], Lynette Bowes[3,4], Robert Rutledge[5,2], Ketan Kulkarni[1,2], Daniel McNeely[1,2], and Craig Erker[1,2]; [1]IWK Health Centre, Halifax, Canada, [2]Dalhousie University, Halifax, Canada, [3]Janeway Children's Health Centre, St. John's, Canada, [4]Memorial University, St.John's, Canada, [5]Queen Elizabeth II Health Sciences Centre, Halifax, Canada

Background: Diagnostic delays in pediatric neuro-oncology is a subject of distress for families and providers. We aimed to evaluate the symptom diagnostic interval (SDI) and influencing variables for children with CNS tumors. Methods: This retrospective study analyzed 210 patients diagnosed from 2001–2018 and managed at the tertiary care facility in Halifax, Canada. SDI was defined as time from first symptom until tissue diagnosis or, if not available, imaging diagnosis. Non-parametric tests were used to compare SDI between groups. Results: Median SDI was 12.4 weeks (IQR 4.3–30), longer than 7 other studies of 1308 children reporting medians of 4.5–10 weeks ($p < 0.01$). Most common tumors and their median SDI included low-grade glioma (LGG) (n=97, 46%; 17.9 weeks), medulloblastoma (n=31, 15%; 8.7 weeks), high-grade glioma (HGG) and DIPG (n=23, 11%; 5.6 weeks), and ependymoma (n=13, 6%; 13.6 weeks). The most common initial reported symptom included headache (n=63; 30%), nausea/vomiting (n=27, 18%), seizure (n=24, 12%), and visual impairment (n=13, 6.3%). Patients aged 0–3 years had a shorter SDI than patients 10 years and older (SDI 8.7 vs 14.6 weeks; $p = 0.03$). Tumor category showed longer SDI for LGG versus HGG ($p = 0.003$), DIPG ($p = 0.02$), medulloblastoma ($p = 0.03$) and other embryonal tumors ($p = 0.03$). Longer SDI was not associated with increased risk of disease progression for LGG ($p = 0.93$), medulloblastoma ($p = 0.89$), or ependymoma ($p = 0.5$). No difference in SDI was found with regard to diagnosis era, ethnicity, socioeconomic status, or distance to the tertiary care facility. Conclusion: SDI at our centre is longer than previously reported studies. SDI is linked to tumor biology and its relevance within specific tumor groups deserves further investigation given it doesn't appear to predict tumor progression/recurrence, yet families and providers feel distress when delays in diagnosis are perceived.

RARE-02. POLYAMINE PATHWAY INHIBITION IS A POTENT NOVEL THERAPEUTIC STRATEGY AGAINST DIFFUSE INTRINSIC PONTINE GLIOMA

Aaminah Khan[1], Laura Gamble[1], Dannielle Upton[1], Denise Yu[1], Ruby Pandher[1], Chelsea Mayoh[1], Mark R. Burns[2], Murray D. Norris[1,3], Michelle Haber[1], Maria Tsoli[1], and David S. Ziegler[1,4]; [1]Children's Cancer Institute, Sydney, NSW, Australia, [2]Aminex Therapeutics, Inc., Kirkland, Washington, USA, [3]University of New South Wales Centre for Childhood Cancer Research, Sydney, NSW, Australia, [4]Kids Cancer Centre, Sydney Children's Hospital, Sydney, NSW, Australia

Diffuse intrinsic pontine glioma (DIPG) is an aggressive paediatric brainstem tumour, with a median survival of less than 1 year. Polyamines are intracellular polycations that control important aspects of cell growth and are often upregulated in cancer. Difluoromethylornithine (DFMO) is an FDA-approved inhibitor of the enzyme ornithine decarboxylase (ODC1) which is a key driver of polyamine synthesis. We investigated the efficacy of polyamine pathway inhibitors as a therapeutic strategy against DIPG.

We found that there were high over-expression levels of polyamine synthetic enzymes from DIPG primary patient samples and neurosphere cultures. Using alamar blue cytotoxicity and soft-agar clonogenic assays, we found that DFMO inhibited the proliferation of DIPG neurospheres. However, DIPG cells compensated for DFMO inhibition by increasing expression of the polyamine transporter SLC3A2 and subsequently uptake of polyamines. Addition of polyamine transporter inhibitor AMXT 1501 to DFMO led to synergistic inhibition of DIPG proliferation *in vitro*. Consistent with the *in vitro* results, the combination of DFMO and AMXT 1501 significantly prolonged the survival of mice bearing 3 different DIPG orthografts with at least 2/3 of the animals surviving up to 160 days. Addition of irradiation further improved the survival of mice treated with DFMO and AMXT 1501. Differential expression analysis showed that the polyamine transporter, SLC3A2, was significantly overexpressed in DIPG and other paediatric brain tumours including high grade gliomas compared with normal brain tissue. Our results suggest that DIPG tumours are exquisitely sensitive to polyamine inhibitors, and that dual blockade of polyamine synthesis and transport is a promising novel therapeutic strategy. AMXT 1501 is currently in clinical development, and following completion of an adult Phase 1 trial, a clinical trial of AMXT 1501 + DFMO for DIPG patients is planned through the CONNECT consortium.

RARE-03 CENTRAL NERVOUS SYSTEM TUMORS IN CHILDREN WITH NEUROFIBROMATOSIS TYPE 1, A COHORT FROM A NATIONAL PEDIATRIC ONCOLOGY CENTER

Kim Vandenput[1,2], Lisethe Meijer[1], Netteke Schouten-van Meeteren[1]; [1]Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands, [2]Radboud University Medical Center, Nijmegen, The Netherlands

Approximately 15% of the children with Neurofibromatosis type 1 (NF1) develop a central nervous system (CNS) tumor, predominantly optic pathway glioma. However, other brain tumor types are also frequent, resulting in a heterogenous population regarding tumor type, symptoms and treatment. Even though many tumors are indolent, clinical deterioration or radiological progression requires surveillance and treatment. Pediatric oncology care in the Netherlands has been centralized into the Princess Máxima Center since June 2018, providing care for the majority of Dutch NF1 CNS tumor patients. This retrospective cohort study describes the course of disease in NF1 patients with a CNS tumor diagnosed between 2005–2020, based on data from patient files. The population consisted of 95 patients (48 males), median age at diagnosis 4.3 (range 0.8–17.2) and 12.6 (range 2.9–19.9) years at follow up, 27% familiar NF1, mostly nonsense or frameshift mutations. Neurological and/or visual symptoms were present in 64 (67.4%) patients. 63.6% of the tumors was in the optic pathway, 9.1% in the cerebellum. Biopsy in 19/95 revealed 1 ependymoma and 18 low grade glioma, with rarely additional molecular changes besides NF1. Kaplan Meier median PFS was 24 months (range 3–174.5, n=65) in symptomatic presenting patients, 34 months (range 5–165, n=20) in asymptomatic patients with abnormal ophthalmological and/or neurological exam and 67.3 months (range 7–130, n=10) in asymptomatic patients without abnormalities at exam. Treatment was indicated in 53 (55.8%), predominantly chemotherapy (n=49), with substantial toxicity. Carboplatin allergy was seen in 29/44 (65.9%) patients, peripheral neuropathy in 21/46 (45.7%) patients receiving vincristine, and 5/10 patients receiving irinotecan and bevacizumab ended treatment early due to toxicity. In conclusion: analysis of our extensive cohort of NF1 patients with a CNS tumor indicates the relevance of regular screening of NF1 patients without complaints and critical surveillance and systematical documentation of treatment toxicity.

RARE-04. IMPACT OF LIVE, VIRTUAL EDUCATIONAL SYMPOSIA ON PEDIATRIC NEURO-ONCOLOGIST, NEURO-ONCOLOGIST, AND NEUROSURGEON CONFIDENCE, KNOWLEDGE, AND INTENTION TO EMPLOY TARGETED MEDICAL THERAPIES FOR THEIR PATIENTS WITH NEUROFIBROMATOSIS TYPE 1

Bryan Taylor[1], Rebecca Weaver[1], Andrea Gross[2], Bruce Korf[3], and Jaishri Blakeley[4]; [1]CEC Oncology, Lexington, KY, USA, [2]National Institutes of Health, Bethesda, MD, USA, [3]University of Alabama at Birmingham, Birmingham, AL, USA, [4]Johns Hopkins University, Baltimore, MD, USA

Historical treatment options and management strategies for neurofibromatosis type 1 (NF1) have been limited, with a relative paucity of clinical studies and the traditional paradigm focused on an ineffectual, and possibly even harmful, trimodal combination of radiation, surgery, and surveillance. Fortunately, an emerging preponderance of trial data supporting the use of targeted medical therapies, including MEK inhibitors and multikinase TKIs, is expanding the stale treatment paradigm and broadening horizons for patients. Given the profound novelty of this paradigmatic shift in NF1 management, it is imperative that timely, adaptive, and evidence-based educational initiatives be developed and delivered to the interdisciplinary neuro-oncology treatment team in an effort to bridge both learning and practice gaps. With an appreciation of the intrinsically multi-system nature of NF1, which necessitates a longitudinal treatment approach encompassing the totality of the multidisciplinary team, CEC Oncology designed and tailored targeted NF1 educational activities to improve confidence, advance knowledge, and promote enhanced utilization of targeted medical therapies among pediatric neuro-oncologists, neuro-oncologists, and neurosurgeons who manage patients with NF1. We conducted two independent satellite symposia, one at the 2020 Society for Neuro-Oncology (SNO) Annual Meeting and another at the 2020 AANS/CNS Section on Pediatric Neurological Surgery (PNSS), and achieved robust educational outcomes across Moore's Levels 1–5. There were notable statistical advancements in clinician confidence, knowledge, and intention to employ targeted medical therapies for NF1-related symptomatic, inoperable plexiform neurofibromas from pre-activity to post-activity assessment, and many of these improvements were retained at 6-week follow-up analysis. In conclusion, our outcomes data evidence the critical need for responsive educational activities in the NF1 treatment space, especially as trial data continue to galvanize evolution of this novel pharmacologic armamentarium. Such activities possess the capacity to improve clinician confidence, advance knowledge, and promote utilization of targeted medical therapies in NF1, thereby optimizing patient outcomes.

RARE-05. ANAPLASTIC ASTROCYTOMA AND OLIGODENDROGLIOMA PRESENTING AS SIMULTANEOUS PRIMARY BRAIN TUMORS IN A PEDIATRIC PATIENT: THE FIRST KNOWN REPORT OF A RARE CONDITION

Amber Brown, and Stanley Chaleff; Maine Medical Center, Portland, ME, USA

Multiple metastatic brain tumors and multiple histologically identical primary brain tumors have been reported in adults and children. The concurrent presence of multiple histologically distinct primary brain tumors is rare without prior chemotherapy, radiotherapy, or phacomatosis. Exceedingly rare are simultaneous histologically distinct primary brain tumors in children without therapeutic or genetic predisposition, with only five previously reported cases. Gliomas are the most common primary brain tumor in adults and children. Gliomas encompass a heterogenous group characterized by astrocytic, oliogodendroglial, and ependymomal histology, further subdivided into pathologic World Health Organization (WHO) grades I to IV. In children, grade I astrocytomas are the most common, with grade III astrocytomas (anaplastic astrocytomas) and oligodendrogliomas being rare. We report a case of simultaneous anaplastic astrocytoma and grade II oligodendroglioma in a pediatric patient. A previously healthy 6-year-old female presented with persistent headaches. Initial magnetic resonance imaging (MRI) demonstrated non-enhancing right frontal lobe and left peri-thalamic lesions without mass affect. Serial MRIs showed progression of both lesions, prompting frontal lobe biopsy, which revealed a grade II oligodendroglioma. The patient was started on standard low-grade glioma chemotherapy, which was stopped due to an allergic reaction. Following chemotherapy cessation, both lesions increased in size, and the peri-thalamic lesion demonstrated new heterogenous enhancement. The patient underwent gross-total resection of the peri-thalamic lesion and repeat biopsy of the frontal lobe lesion. Pathology confirmed the frontal lobe lesion to be a grade II oligodendroglioma and revealed the peri-thalamic lesion to be an anaplastic astrocytoma. The tumors were additionally proven molecularly distinct. The patient responded well to cranial radiotherapy and standard high-grade glioma chemotherapy. To the best of the authors' knowledge, this is the first case of simultaneous anaplastic astrocytoma and oligodendroglioma in a child, increasingly unique given the histological and molecular rarity of the tumors in pediatric patients.

RARE-06. CLINICAL BURDEN AMONG PATIENTS WITH NEUROFIBROMATOSIS TYPE 1 (NF1) AND PLEXIFORM NEUROFIBROMA (PN) IN THE UNITED STATES (US)

Xiaoqin Yang[1], Hyun Kyoo Yoo[2], Suvina Amin[3], Wendy Cheng[4], Heather Sipsma[4], Sanjana Sundaresan[4], Lujia Zhang[4], and Mei Sheng Duh[4]; [1]Merck & Co., Rahway, NJ, USA, [2]AstraZeneca, Cambridge, UK, [3]AstraZeneca, Gaithersburg, MD, USA, [4]Analysis Group Inc., Boston, MA, USA

Background: Plexiform neurofibromas (PNs) occur in 30–50% of pediatric patients with neurofibromatosis type 1 (NF1), often resulting in debilitating pain and dysfunction. Real-world evidence describing the clinical disease burden among these patients is limited. This study aimed to characterize this burden among pediatric NF1 PN patients in the United States (US). Methods: Caregivers of 82 patients ages 2–18 years with NF1 PN in the US who were treatment naïve or new users of selumetinib (defined as ≤1 month of use) were recruited through the Children's Tumor Foundation to participate in an online cross-sectional survey from December 1, 2020 through January 14, 2021. Participants responded to items measuring patient demographic and clinical characteristics and the burden of debulking sur-