defines the rhabdoid tumors predisposition syndrome. Penetrance is almost complete and the vast majority of germline alterations of *SMARCB1* are acquired de novo but rare familial cases with a healthy carrier have also been described. Since the advent of more sensitive molecular analysis technologies such as next-generation sequencing (NGS), the number of mosaicisms of genes involved in genetic diseases discovered from blood samples has increased considerably. The aim of our study was to explore the mosaicisms of *SMARCB1* in the blood 1/ of children with rhabdoid tumors with at least one alteration of *SMARCB1* previously identified in the tumor but not found in the blood with old-fashioned low-sensitivity technologies and 2/ in parents of children with heterozygous germline alteration of *SMARCB1*. We analyzed a custom NGS panel which covers the *SMARCB1* gene with an average depth of 1.500X on blood samples of 111 children with rhabdoid tumors and 32 parents collected at the Institut Curie since 1999. The mosaicism rate found in index cases was 11.7% (13/111) and 3.1% (1/32) in parents. The variant allele frequency vary from 0.8% to 12.9%. Our results also indicate to be cautious about the possible confounding effect of circulating tumor DNA. This hitherto underestimated *SMARCB1* mosaicism rate should motivate an optimization of the genetic counseling as well as the oncological monitoring of these children and thus have a significant medical impact given the catastrophic prognosis of rhabdoid tumors.

ATRT-22. OUTCOMES FOR CHILDREN WITH RECURRENT ATYPICAL TERATOID RHABDOID TUMOR: A SINGLE INSTITUTION STUDY WITH UPDATED MOLECULAR AND GERMLINE ANALYSIS

Steven S. Carey, Jie Huang, Jason R. Myers, Roya Mostafavi, Brent Orr, Layna H. Michalik, Paul Klimo, Jr., Frederick Boop, Kim E. Nichols, Thomas Merchant, David W. Ellison, Giles W. Robinson, Arzu Onar-Thomas, Amar Gajjar, Santhosh Upadhyaya; St. Jude Children's Research Hospital, Memphis, TN, USA

BACKGROUND: Children with recurrent atypical teratoid rhabdoid tumor (recATRT) who fail frontline therapies have dismal outcomes. The association of ATRT molecular groups (SHH, TYR and MYC) and presence of underlying cancer predisposition with survival post-recurrence (postRD) is unknown. METHODS: We previously reported outcomes from a single-institution retrospective study of children <21 years with recATRT treated at St. Jude Children's Research Hospital from 2000 to 2020. Herein we report updated progression-free survival (PFS2: time from initial recurrence to subsequent first progression) and overall survival (OSpostRD: time from initial recurrence to death/last follow-up) outcomes by molecular groups determined by tumor DNA methylation and by germline SMARCB1/SMARCA4 alterations (GLA). RESULTS: Median age and time from initial diagnosis to recurrence for 64 eligible patients were 2.1 years (range: 0.5-17.9 years) and 5.4 months (range: 0.5–125.6 months), respectively. The 2- and 5-year PFS2 and OSpostRD were 3.1% (±1.8%)/1.6% (±1.1%) and 20.3% (±4.8%)/7.9% (±3.8%), respectively. PFS2 did not differ by molecular groups (p=0.210) for 42 participants with available data (MYC=11, SHH=21, TYR=10). Children with TYR group had a better 2-year OSpostRD [60.0% ±14.3% (TYR) vs. 18.2% ±9.5% (MYC) or 4.8% ±3.3% (SHH)] (p=0.018). In univariate analyses, OSpostRD was also better with older age at diagnosis (≥ 1 year vs <1 year; p=0.03), female gender (p=0.008), and metastatic site of recurrence compared to local or combined sites of disease (p<0.001). OSpostRD did not differ for those with positive GLA (n=12) compared to those without (n=21) (p=0.231). Only 6 children (9.4%) (TYR=4, SHH=1, NA=1) were alive at median follow-up of 7.7 years from recurrence. CONCLUSION: Children with recATRT have extremely poor outcomes. Older age at diagnosis, female gender, TYR group, and metastatic site of initial recurrence were associated with longer survival in our study. These results reinforce the dire need for better therapeutic options.

ATRT-23. SIRT2 COOPERATES WITH SMARCB1 TO INDUCE A DIFFERENTIATION BLOCK IN ATRT

Irina Alimova[1], Dong Wang[1], Angela Pierce[1], Senthilnath Lakshmanachetty[2], Eric Prince[3,4], Etienne Danis[1], Natalie Serkova[5], Krishna Madhavan[1], Ilango Balakrishnan[1], Min Yang[6], Henning Lin[6], Nicholas Foreman[1,7], Sujatha Venkataraman[1,7], Rajeev Vibhakar[1,7]; [1]Department of Pediatrics University of Colorado Denver, Anschutz Medical Campus, Aurora, Colorado, USA. [2]Department of Pediatrics, University of Colorado Denver Anschutz, Aurora, Colorado, USA. [3]Department of Biostatistics and Informatics University of Colorado Denver Anschutz Medical Campus, Aurora, Colorado, USA. [4]Department of Neurosurgery University of Colorado Denver Anschutz Medical Campus, Aurora, Colorado, USA. [5]Department of Radiology University of Colorado Denver, School of Medicine, Aurora, Colorado, USA. [6]Department of Chemistry and Chemical Biology, Cornell University, Ithaca, NY, USA. [7]Morgan Adams Foundation Pediatric Brain Tumor Research Program, Children's Hospital Colorado, Aurora, Colorado, USA

Atypical Teratoid Rhabdoid Tumor is a highly aggressive pediatric brain tumor with poor prognosis driven by loss of the chromatin remodeling factor SMARCB1 that is responsible for determining cellular pluripotency and lineage commitment. The mechanisms by which SMARCB1 deletion results in tumorigenesis remain unclear. We investigated the effect of SIRT2 inhibition in ATRT which was identified as a primary dependency in ATRT. SIRT2 inhibition with shRNA or Thiomyristoyl (TM) decreased ATRT cell growth, inhibited clonogenic potential and leaded to the cell cycle arrest. SIRT2 inhibition effectively suppresses pluripotency-associated genomic programs, significantly changed stem cell frequency, decreased tumor-sphere formation of ATRT cells and attenuated tumor cell self-renewal. In vivo SIRT2 inhibition decreased oncogenic markers and increased accumulation neuronal differentiation markers. Furthermore, SIRT2 induced apoptosis, decreased tumor growth and prolonged survival in orthotopic xenograft models. Single-cell RNA transcriptome analysis of xenoftaft tumors reveals elimination of tumor cells expressing stem cell genes and expansion of tumor cells expressing differentiated genes following TM treatment in ATRT. We demonstrated that SIRT2 inhibition is a molecular vulnerability in SMARCB1-deleted ATRT.

ATRT-24. CDK7 INHIBITION IN AT/RT

Andrew Morin[1], Darya Wodetzki[2], Bethany Veo[2], Angela Pierce[2], Shadi Zahedi[3], Michele Crespo[2], Sujatha Venkataraman[2], Rajeev Vibhakar[2], Jean Mulcahy-Levy[1]; [1]Children's Hospital Colorado, Denver, CO, USA. [2]University of Colorado Anschutz Medical Center, Denver, CO, USA. [3]University of Colorado Anschutz Medical Center, denver, CO, USA

Atypical teratoid/rhabdoid tumors (AT/RT) are CNS tumors with a 5-year survival of ~35%. AT/RT is characterized by loss-of-function mutations in the SMARCB1 component of the SWI/SNF (SWItch/Sucrose Non-Fermentable) complex. Based on preliminary CRISPR-Cas9 gene essentiality screen results identifying AT/RT vulnerabilities, we hypothesized that interaction between CDK7 and the SWI/SNF complex via SMARCB1 provides a potential target to improve clinical survival of patients. CDK7 expression was identified by microarray in AT/RT, medulloblastoma, glioblastoma and normal brain. Established cell lines (BT12, BT16, CHLA06), patient derived lines (MAF-737, MAF-1298, MAF-1337), normal human astrocytes (NHA) and NIH3T3 mouse embryonic fibroblast cells were utilized for *in vitro* response to CDK7 inhibition. Murine cerebellar xenografts of MAF-737 were utilized to evaluate genetic and pharmacologic response to CDK7 inhibition. The NCI Approved Oncology Drugs (AOD-9) Panel was evaluated with an IC25 dose of CDK7 inhibitor THZ2 to identify potential synergistic combinations. CDK7 is up-regulated in AT/RT compared to other brain tumors or normal brain. *In vitro*, AT/RT cells are highly susceptible to CDK7 pharmacologic inhibition with nM IC50 levels. AT/RT cells with shRNA against CDK7 implanted *in vivo* show significantly reduced growth. Evaluation of *in vivo* tumors treated with THZ2 demonstrate decreased Ki-67 and reduced pRBP1 demonstrating effective inhibition of the target as well as a decrease in cell proliferation. Combination therapy of THZ2 with the AOD-9 Panel found significant synergy with antimetabolite therapies, specifically pemetrexed, pralatrexate, and methotrexate. There was no synergy with other standard chemotherapy. Our findings demonstrate that CDK7 is highly expressed in AT/RT and necessary for proliferation of AT/RT cells, suggesting it as a potential therapeutic target. Antimetabolites, which are currently used in several AT/RT protocols, synergized with CDK7 inhibition offers a potential future combination therapy for patients.

ATRT-25. CERVICAL ATYPICAL TERATOID RHABDOID TUMOR IN PEDIATRIC PATIENTS: A STUDY OF THE LAST DECADE

Amanda Cyntia Lima Fonseca Rodrigues[1], Letícia dos Santos Louro[2], Maria Eduarda Geddo Kostakis[3], Milena Henriques Fialho[4], Kananda Oliveira Garcia Ruiz[4], Beatriz Patriota Saraiva Costa[3], Monique Benemérita Vilela Gomes[5]; [1]Universidade Positivo, Curitiba, Paraná, Brazil. [2]Universidade Paulista, Santos, São Paulo, Brazil. [3]Universidade de São Caetano do Sul, São Caetano do Sul, São Paulo, Brazil. [4]Universidade Federal de São João Del Rei, São João Del Rei, Minas Gerais, Brazil. [5]Universidade Federal do Piauí, Picos, Piauí, Brazil

BACKGROUND: Atypical rhabdoid teratoid tumor (AT/RT) is an extremely rare primary tumor of the central nervous system (CNS) with a high incidence in children under 3 years of age. The existing literature involving this tumor is scarce, even though AT/RT is considered one of the most malignant brain tumors due to its aggressive course and short survival time, which generally does not exceed 1 year. METHODS: The "PubMed" database was used for this study using the MeSH Terms "Child" and "Atypical Teratoid Rhabdoid Tumor" and the filter "Case Reports" in order to carry out a study with the clinical cases of the last decade and the involvement of this tumor in the cervical region of pediatric patients. 96 articles were found, however, only 10 articles were selected for this review. RESULTS: It is possible to affirm that the cases of AT/RT are found in greater numbers in children under 3 years of age and are predominantly located in the cervical region when they affect the spinal cord. In addition, MRI usually shows a solid heterogeneous mass that results in the appearance of symptoms, since the mass compresses the conus medullaris and consequently generates pain in the spine. The prognosis is reported to be a difficult one and the median patient survival time is less than one year. CONCLUSION: Therefore,