consolidation chemotherapy and/or radiation treatment, patients were enrolled and commenced on panobinostat as a continuous daily oral dose starting at 10mg/m^2/day, with a three-week wash out period between therapies. Real-time acetylation status, measuring acetylated H4 on PMNC, was performed to determine the pharmacodynamics of panobinostat at different dosing levels. Patients were monitored for toxicity; dose reductions were in decrements of 2mg/m^2/day. RESULTS: A total of 13 patients with newly diagnosed ATRT/MRT and one patient with relapsed MRT have been enrolled. The average age at enrollment was 3.6 years (range 0.8-6.8 years). The mean treatment duration was 206 days (13-344 days). Currently, six patients (42.9%) remain on study with a mean study duration of 531 days (range 13-895 days). 6/14 patients (42.9%) were removed due to disease progression at a mean study duration of 245 days (44-560 days). 2/14 patients (14.3%) withdrew due to toxicity. 12/14 patients (85.7%) required dose reductions. The main toxicities were thrombocytopaenia and leukopaenia (Grade III-IV). Real-time pharmacodynamic assessment of panobinostat, at a dose as low as 6mg/m^2/day resulted in significant acetylation of histone H4 in PMNC. CONCLUSIONS: Treatment with low dose panobinostat is well tolerated in infants and children with MRT/ATRT, with significant acetylation of histone H4 in PMNC.

ATRT-18. ATYPICAL TERATOID/RHABDOID TUMOR IN CHILDREN: CASE REPORTS FROM INDONESIA

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Atypical teratoid/rhabdoid tumor (AT/RT) of the central nervous system is a sporadic and highly malignant tumor that usually affects very young children and is typically deadly despite very aggressive treatment. The optimal treatment for AT/RT remains unclear, including surgery, radiotherapy, and chemotherapy. Here we report cases of AT/RT in Indonesia. Case 1: A three-year-old girl came with worsening intermittent headaches with projectile vomiting, progressive and insidious right spastic hemiparesis, and slowly progressive weight loss three months before admission. She had septate multiloculated hydrocephalus. Head MRI demonstrates a solid lobulated mass with heterogeneous enhancement and MRS shows an aggressive metabolite pattern, arising from posterior fossa extending into the cerebellum and cerebellopontine angle, causing severe obstructive hydrocephalus. She underwent tumor resection with a midline suboccipital approach, then continued with craniospinal irradiation with dose of 36 Gy in 20 fractions then followed by 18 Gy in 10 fractions booster to posterior fossa, making the total dose to posterior fossa (the tumor) to be 54 Gy. Case 2: A twenty-month-old baby with a history of recurrent seizures, tremors, and less activity in the last two months. She had spasticity with hyperreflexia. She has been referred to our center for further evaluation and management after biopsy and VP shunt surgery at the previous hospital. Head CT scan demonstrates a large solid heterogeneous mass in the right hemisphere cerebral, causing midline shift and hydrocephalus. After the VP shunt was repaired, she underwent Head Start III chemotherapy protocol cycle 1. Both pathology examinations of the patients revealed a hypercellular tumor with prominent hyperchromatic nucleoli and loss of INI-1 staining on immunohistochemistry consistent with an ATRT diagnosis. Unfortunately, both patients died due to severe sepsis after treatment. Although AT/RT has become increasingly recognized, prognosis of ATRT is generally unfavorable, especially in developing countries.

ATRT-19. FUNCTIONAL GENOMICS REVEAL DISTINCT MODULATORS OF RESPONSE TO CDK4/6 INHIBITORS IN ATRTS

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Brain tumors are the leading cause of cancer-related deaths in children, and atypical teratoid rhabdoid tumors (ATRTs) are among the most common aggressive brain tumors in infants. With no standard-of-care treatment so far, ATRTs continue to have relatively low survival estimates, illustrating the urgent need for more efficacious treatment options. We have previously used genome-wide CRISPR/Cas9 knockout screens in combination with small-molecule drug assays to identify targetable vulnerabilities in ATRTs. CDK4/6 inhibitors, among the most promising drugs in our study with direct translational potential, are capable of inhibiting tumor growth due to mutual exclusive dependency of ATRTs on either CDK4 or CDK6. We here used genome-wide loss-of-function and gain-of-function strategies to identify modulators of response to CDK4/6 inhibition in ATRTs. Of note, while some well-known resistance mechanisms such as loss of RB1 or FBXW7 are shared by ATRT cell lines, we have also identified modulators of response to CDK4/6 inhibition with opposing effects across ATRT cell lines. As such, loss of AMBRA1, a recently described master regulator of D type cyclins, can either oppose the effects of or synergize with CDK4/6 inhibitors based on the cellular background. We are currently using a proteomics approach to further delineate the mechanism driving this functional heterogeneity of AMBRA1 in ATRTs. Our study will therefore provide deeper insights into the response of ATRTs to CDK4/6 inhibitors, which represent one of the most promising class of targeted agents for the treatment of ATRTs.

ATRT-20. NOVEL PROGNOSTIC MOLECULAR SIGNATURES FOR IMPROVED RISK-CLASSIFICATION OF ATYPICAL TERATOID RHABDOID TUMOURS

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Malignant Rhabdoid Tumours (MRT) are aggressive paediatric malignancies seen in the central nervous system (Atypical Teratoid Rhabdoid Tumours (ATRT)), and kidney and other soft tissues (Extra-cranial Rhabdoid Tumours (ECRT)). With current therapies often proving ineffective and a lack of clear prognostic associations with consensus subgroups, we explored the possibility of using prognostic molecular signatures to further identify the biological characteristics of high risk ATRT patients. By employing a cross-validated feature selection method the methylation profiles of 121 MRT patients were analysed with clinical data to obtain meta-CpG signatures associated with prognosis for ATRT, ECRT and MRT. The relationship between these meta-CpG signatures and the consensus subgroups were further explored, along with the correlation of meta-CpGs with gene expression to establish biological significance. By selecting CpGs for their ability to predict survival this method obtained three novel prognostic methylation signatures which predict MRT outcome (ATRT-5, ECRT-14 and MRT-42). These signatures are independent of molecular subgroup and each signature was significantly associated with overall survival (OS) and event free survival (EFS) in their respective cohorts ($p<0.001$). Both ATRT-5 and MRT-42 maintained their significant association with OS in an independent ATRT cohort (n=64) and each meta-CPG signature is prognostically independent of other major clinical risk factors (e.g. receipt of radiotherapy and presence of metastases). Biologically, individuals with high-risk methylation signatures showed a gene expression profile suggestive of higher proliferative rates and tumours with low-risk scores in ATRT-5 and MRT-42 had an upregulated inflammatory response and increased immune infiltration. Combining these meta-CpGs with other significant clinical risk-factors produced high performing multivariate Cox-models enabling us to propose new stratification models for ATRT and MRT patients. These subgroup-independent prognostic signatures represent a distinct biology in ATRT and, if validated in prospective studies, could progress the use and efficacy of precision-based medicine in this therapeutically challenging disease.

ATRT-21. CONTRIBUTION OF GERMLINE MOSAIC ALTERATIONS OF SMARCB1 IN RHABDOID TUMOR PREDISPOSITION SYNDROME

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Rhabdoid tumors are rare and aggressive tumors that usually arise in very young children. They are characterized by a bi-allelic inactivation of the *SMARCB1* gene. Although the majority of alterations of *SMARCB1* are acquired in tumors, a heterozygous germline alteration is seen in one third of patients and

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

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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

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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

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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

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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,