well as alterations in DNA damage response pathways, cell cycle checkpoints, miRNA transcription, and numerous proliferative factors. THZ2 penetrates the blood brain barrier (BBB), is well tolerated, and results in prolonged survival in murine xenograft models of AT/RT. CDK7 inhibition also synergizes with a number of currently-approved oncology drugs, as well as with ionizing radiation, in order to inhibit AT/RT growth and viability.

ATRT-21. RHABDOID PREDISPOSITION SYNDROME: REPORT OF MOLECULAR PROFILES AND TREATMENT APPROACH IN THREE CHILDREN WITH SYNCHRONOUS ATYPICAL TERATOID/ RHABDOID TUMOR AND MALIGNANT RHABDOID TUMOR

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BACKGROUND: Rhabdoid predisposition syndrome is characterized by germline alterations in *SMARCB1* or *SMARCA4*, leading to synchronous or metachronous central nervous system (CNS) and extra-CNS rhabdoid tumors. Rare survivors have been reported to date. METHODS: We describe the molecular profiling and treatment regimen of three patients with synchronous atypical teratoid/rhabdoid tumor (ATRT) and malignant rhabdoid tumor of the kidney (MRT-K). All patients underwent radical nephrectomy of the kidney, and gross total resection of the primary CNS tumor was achieved for two patients. An intensive chemotherapy regimen was administered; an induction phase based on the modified Third Intergroup Rhabdomyosarcoma Study (IRS-III) for ATRT followed by a consolidation phase with three cycles of high-dose chemotherapy and autologous hematopoietic progenitor cell rescue, without irradiation. All three patients were enrolled on an institutional comprehensive genomic profiling protocol. RESULTS: A germline focal 22q deletion, including *SMARCB1,* was detected in two patients, while the third patient had a maternally-inherited heterozygous frameshift variant in *SMARCB1*. Somatic loss of heterozygosity of 22q was identified in all patients, resulting in biallelic inactivation of *SMARCB1*. Divergent tumor subgroups were described using DNA methylation. The three MRT-K samples were classified as MYC subtype. One ATRT was classified as SHH while the other as TYR. One patient is currently three years off-therapy without evidence of disease, while the other two patients have completed the consolidation phase without recurrent disease. CONCLUSION: Molecular profiling of CNS and extra-CNS rhabdoid tumors revealed different epigenetic subgroups. An intensive multimodal therapeutic approach without irradiation may achieve prolonged survival.

ATRT-22. HIGH-THROUGHPUT DRUG SCREENING OF FDA-APPROVED CANCER DRUGS REVEALS POTENTIAL THERAPEUTIC APPROACHES FOR ATYPICAL TERATOID RHABDOID TUMOUR

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Atypical teratoid/rhabdoid tumors (ATRT), are the most common brain tumor in children under the age of 1 year with an overall survival of ~17%. Like extracranial rhabdoid tumors, ATRT is exclusively characterized by bi-allelic loss of *SMARCB1*, a critical subunit of the SWI/SNF chromatin remodeling complex, implicating epigenetic deregulation in the pathogenesis of disease. We have previously shown the ability of the histone deacetylase inhibitor, panobinostat, to mimic SMARCB1-mediated SWI/SNF functions in extracranial rhabdoid tumors to inhibit tumor growth by driving multi-lineage differentiation *in vitro* and *in vivo*. Whether this also applies to ATRT is unknown. Using a panel of human-derived ATRT cell lines, representing defined molecular subgroups, we have shown that prolonged treatment with panobinostat at nanomolar concentrations results in markedly reduced clonogenicity, and increased senescence, preceded by increased H3K27 acetylation, decreased H3K27 trimethylation and EZH2 expression. To determine potentially synergistic therapies, we performed high-throughput drug screening of 622 compounds already in advanced clinical trials or FDA-approved for other indications, across our panel of ATRT models and identified 30 common compounds, which decrease cell viability by >50%, with no effect on neural stem cell controls and 12 compounds which demonstrated subgroup specificity, highlighting the necessity to consider therapies in the molecular context. In addition to HDACi, consistent with our panobinostat in vitro findings, inhibitors of CDK, survivin and PI3K were the top hits. *In vitro* and *in vivo* validation of these compounds alone, and in combination with panobinostat is ongoing.

ATRT-23. THE DUAL MTORC1/2 INHIBITOR SAPANISERTIB DISRUPTS THE NRF2-MEDIATED STRESS RESPONSE AND COMBINES SYNERGISTICALLY WITH THE BH3 MIMETIC OBATOCLAX TO EXTEND AT/RT SURVIVAL

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Atypical teratoid/rhabdoid tumors are aggressive infantile tumors highly resistant to intensive therapies. We aim to identify and target critical factors driving this therapy resistance to improve AT/RT survival. Analysis of publically available RNASeq on 32 AT/RT identified elevated expression of NRF2 (median expression 40.78, normal brain 18.81). NRF2 is a master regulator of cell's stress response whose expression is correlated with therapy resistance and poor survival. NRF2 activation is sensitive to mTOR activity and is a biomarker predicting response to the dual mTORC1/2 inhibitor, Sapanisertib (TAK228, INK128). We performed RNASeq on 4 human-derived AT/RT cell models after Sapanisertib treatment. Pathway analysis reveals disruption of the NRF2-mediated stress response (-log p value 0.39, Z-score 1.0). As a result, Sapanisertib decreases ROS scavengers like glutathione (Metabolite analysis UHPLC-MS, *t*-test $p<0.05$) and induces a pro-death phenotype (decreased MCL-1 expression, western blot; gene-expression analysis, RNASeq). The brain-penetrant BH3 mimetic Obatoclax increases ROS generation and induces apoptosis (MUSE oxidative stress and ANNEXIN V assays, *t*-test $p<0.05$). These complementary mechanisms of action synergize to induce high rates of cell death (MUSE ANNEXIN V assay, ANOVA $p<0.05$, C-PARP western blot, Compusyn Synergy analysis CI<1.0) and slow cell growth (MUSE Cell viability, ANOVA $p<0.05$). Once-weekly treatments of Sapanisertib combined with Obatoclax in orthotopic mouse models of AT/RT are well tolerated, slow tumor growth (bioluminescence imaging) and significantly extend median survival from 35 to 55 days (Log-rank $p<0.05$). These findings support a new clinical trial aimed at improving AT/RT survival.

ATRT-24. CELL SURFACE PROTEOME ANALYSIS OF ATRT IDENTIFIES TARGETS FOR IMMUNOTHERAPY

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Atypical teratoid rhabdoid tumor (ATRT) is a rare and fast-growing childhood tumor of the brain and spinal cord. While the recent advances in DNA and RNA sequencing have given deep insights into the biology of cancer, about 90% of ATRTs harbor a single deletion which leads to uncontrolled tumor growth. The lack of targetable genetic abnormalities in ATRT makes it a tough target for therapy and hence radical new approaches are required to develop a treatment. In many cases, the gene expression profile alone DOES NOT represent the presence of the gene product on the surface and cannot detect post-translational modifications such as the addition of sugars which are essential for the interaction of surface proteins with the tumor microenvironment. The ability to escape from surveillance by the immune system is regarded as one of the essential hallmarks of cancer cells. Here we carried out a comprehensive unbiased large-scale surface receptor profiling using high throughput multicolor flow cytometry on surgically resected ATRT patient samples, primary ATRT cell lines, and patient-derived xenograft models. By multiplexing primary samples with antibodies for CD31, CD45, CD11b, CCR2, Cx3cr1, and CD4, and CD8 we eliminated endothelial and immune cells from analysis while also identifying immune populations within the tumor. We identified increased surface expression of CD44, CD146, CD59, CD151, and CD276. These were validated in our screening of primary tumor samples. A combination of CAR-T cell and function-blocking monoclonal antibody approaches have been tested to verify the proof of principle of this approach.

ATRT-25. INTEGRATED QUANTITATIVE SWATH-MS PROTEOMICS ANALYSIS OF ATRTS UNCOVERS NEW THERAPEUTIC OPPORTUNITIES

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