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INTRODUCTION: Malignant rhabdoid tumors (MRT) are highly aggressive neoplasias mostly affecting young children. They are classified as rhabdoid tumors of the central nervous system (ATRT, atypical teratoid rhabdoid tumor), rhabdoid tumors of the kidney (RTK) or extracranial rhabdoid tumors arising from any soft tissue outside the central nervous system (eMRT, extracranial extrarenal MRT). We report a series of four MRTs with cranial nerve involvement. METHODS: Patients were identified from a cohort of 132 patients with MRT (2017 – 2021), as part of the European Rhabdoid Registry (EU-RHAB). Diagnosis of MRT was confirmed immunohistochemically with loss of INI1 expression. Details regarding symptoms at first presentation, diagnostic staging, genetic findings, therapy and the course of disease are reported. REPORT OF CASES/RESULTS: The series contains two MRT affecting the trigeminal nerve and two cases with third cranial nerve involvement. They were two female and two male patients with a median age of 4.7 years (1-159 months) at diagnosis. Location of the main tumor mass differed between being located intra- and extracerebrally. Metastases at diagnosis occurred in one patient, a germ-line mutation in SMARCB1 was present in two patients. Two patients received therapy according to EU-RHAB recommendations with an incomplete resection, conventional chemotherapy enhanced by intraventricular methotrexate and radiotherapy. Both patients are currently alive with no signs of progression, one of them bearing a germ-line mutation. Two patients received palliative treatment after surgery due to rapid progression. Median overall survival was 17.3 (1.4-53.1) months. CONCLUSION: MRT of the cranial nerves affect the peripheral nervous system in close proximity to the brain, thus forming a unique sub-entity between ATRT and eMRT. The selected cases provide insight into the particular challenge regarding clear classification, diagnostics and therapy.

ATRT-15. PRIMORDIAL GERM CELLS IDENTIFIED AS ONE POTENTIAL CELL OF ORIGIN OF MYC RHABDOID TUMORS

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Rhabdoid tumors (RT) are embryonal neoplasms occurring most frequently in the central nervous system where they are termed atypical teratoid rhabdoid tumor (ATRT). A common hallmark of RT is homozygous loss of the BAF complex subunit SMARCB1. RT patients have a poor prognosis with an overall survival time of 17 months and >60% of patients suffer from relapses. The lack of an optimal treatment strategy could be attributed to the heterogeneity within and between different subgroups of ATRT. Despite the recent advancements in characterizing RT at a molecular level, the cellular origin of RT remains elusive. Thus, this study focused on the identification of the cellular origin of MYC-RT and underlying epigenetic deregulations which account for the cellular heterogeneity in these tumors. We showed that *Smarcb1* abrogation in *Sox2*-positive progenitor cells at E6.5 give rise to RT of the MYC and SHH subgroup in genetically engineered mouse models (GEMM). To uncover distinct cells of origin (COO) for the SHH and MYC subgroups, unbiased computational approaches were used to compare single-cell transcriptomes of GEMMs with single-cell reference maps of murine early embryogenesis. While SHH tumors arise from mid/hindbrain progenitor cells, primordial germ cells (PGCs) emerge as COO of both intracranial and extracranial MYC tumors. PGCs as COO of MYC-RT were validated in vivo by using PGC-specific *Smarcb1* knockout mouse model. We further characterized a deregulated transcriptome in MYC-RT compared to PGCs, which is sustained by a subset of epigenetically driven tumor cells. Deregulated expression of genes driving methylation/demethylation processes in MYC tumors and regression of these tumors upon treatment with decitabine *in vitro* and *in vivo*, indicates that DNA methylation plays a key role in cellular transformation and development of MYC-RT.

ATRT-16. MECHANISMS OF MYELOID CELL-INDUCED RESISTANCE IN AT/RT

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INTRODUCTION: Atypical teratoid/rhabdoid tumor (AT/RT) is a primary pediatric tumor entity of the central nervous system showing intra- and intertumoral heterogeneity concerning the molecular landscape and cellular composition. Myeloid cells are considered key orchestrators of the immunological tumor microenvironment (TME) of AT/RT. Tumor-infiltrating CD68$^+$ macrophages favor chemotherapy resistance and recurrence, and are consequently related to a poor patient outcome. METHODS: Using single-cell RNA sequencing (scRNA-seq) of human and murine AT/RT samples, multiplex immunohistochemistry, depletion of myeloid cells in mouse models and advanced cell culture models for myeloid tumor cell communication, we obtained deeper mechanistic insight into these cell-cell interactions. RESULTS: Infiltrating CD68$^+$ macrophages interact with AT/RT tumor cells generating intermediary hybrid-like cells with autonomous communication properties, increasing the cell heterogeneity of AT/RT. By depletion of myeloid cells in AT/RT mouse models followed by scRNA-seq of tumor and non-tumor samples, we demonstrated that tumor formation is hindered. Furthermore, we give mechanistic insights into how myeloid cells contribute to tumorigenesis. IN CONCLUSION: the dynamic and extensive interactions between tumor cells and myeloid cells do not only potentiate cellular heterogeneity but might also induce cellular plasticity associated with the acquisition of resistance to chemotherapy and seem to be essential for AT/RT development.

ATRT-17. A PHASE II STUDY OF CONTINUOUS LOW DOSE PANOBINOSTAT IN PAEDIATRIC PATIENTS WITH MALIGNANT RHABDOID TUMOURS AND ATYPICAL TERATOID RHABDOID TUMOURS.

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BACKGROUND: Panobinostat treatment has been shown to terminally differentiate malignant rhabdoid tumours (MRT) and atypical teratoid rhabdoid tumours (ATRT) in pre-clinical models. We report results of the open label, phase II study of oral panobinostat in patients with newly diagnosed or relapsed MRT/ATRT. AIMS: To assess the anti-tumour activity of low dose, continuous oral panobinostat as well as its associated toxicities. To assess the biological activity of low dose panobinostat by measuring histone H4 acetylation status in peripheral mononuclear cells (PMNC), and differentiation markers. METHODS: Following primary institutional standard of care induction and

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