CHAPTER SIX

Current advances in the management of atypical teratoid rhabdoid tumors (ATRT)

Michael Angelo Huang[a,*] **and Ashley Margol**[b,c]
[a]Division of Hematology and Oncology, Department of Pediatrics, School of Medicine, Washington University in St. Louis, St. Louis, MO, United States
[b]Department of Pediatrics, Keck School of Medicine, University of Southern California, Los Angeles, CA, United States
[c]Keck School of Medicine, Children's Hospital Los Angeles, Los Angeles, CA, United States
*Corresponding author. e-mail address: huangm@wustl.edu

Contents

1. Introduction 186
2. Epidemiology and clinical presentation 186
   2.1 Rhabdoid tumor predisposition syndrome 187
3. Molecular pathogenesis 188
   3.1 SMARCB1/SMARCA4 inactivation 188
   3.2 Molecular subgroups of ATRT 190
   3.3 Impact of molecular subgroups on prognosis 192
   3.4 Current conventional therapeutic approaches 192
   3.5 Head Start trials 195
   3.6 St. Jude trials 196
   3.7 ACNS0333 196
   3.8 Prognostic impact of specific treatment modalities for ATRT 197
   3.9 Summary recommendations based on prospective upfront ATRT clinical trials 208
4. Innovative mechanism-driven therapeutics for ATRT 208
   4.1 Chromatin remodeling and histone modification 208
   4.2 Cell cycle regulation 213
   4.3 Other associated signaling pathways 217
   4.4 Integrated stress response (ISR) 221
5. Promise of immunotherapeutic strategies for ATRT 223
   5.1 Immune checkpoint inhibition 223
   5.2 Combined epigenetic dysregulation and immune checkpoint inhibition 224
   5.3 Vaccine-based therapy 224
   5.4 Oncolytic viral therapy 225
   5.5 Radioimmunotherapy 225
   5.6 Chimeric antigen receptor (CAR) therapy 228
6. Summary 229
References 229

Advances in Cancer Research, Volume 167
ISSN 0065-230X, https://doi.org/10.1016/bs.acr.2025.08.007

Abstract

Atypical teratoid rhabdoid tumors (ATRT) are rare, often lethal embryonal tumors of the central nervous system (CNS) that primarily affect very young children. Intensive multimodal approaches have resulted in improvements in survival albeit with significant associated toxicity. Recent molecular studies have led to the discovery of SMARCB1 inactivation and resultant BAF47/INI1 loss as the near-universal key genetic event that leads to widespread epigenetic dysregulation. Rarely, SMARCA4 encoding BRG1 is impacted. SMARCB1 and SMARCA4 are core subunits of the SWI/SNF chromatin remodeling complex, which is a fundamental epigenetic regulator of gene transcription. Up to a third of patients diagnosed with ATRT have Rhabdoid Tumor Predisposition Syndrome (RTPS) characterized by germline SMARCB1 (or SMARCA4) alterations. Patients with RTPS are at increased risk of developing synchronous or metachronous rhabdoid tumors outside the CNS. At least three molecular subgroups of ATRT (ATRT-TYR, ATRT-SHH, ATRT-MYC) have been identified through large-scale DNA methylation and transcriptomic studies, with each subgroup having distinct transcriptional, epigenomic and clinicopathologic features. In this book chapter, we will summarize key epidemiological and clinical features of ATRT, review current conventional multimodal regimens, summarize key findings from conducted prospective trials and recently concluded (2020 to present) meta-analyses, as well as discuss emerging targeted treatment approaches that exploit potential therapeutic vulnerabilities of this epigenetically influenced tumor.

1. Introduction

CNS tumors represent the second most common type of childhood (ages 0 to 19 years) cancer and are the leading cause of pediatric cancer related death in developed countries (SEER, 2023). While advances in medical management have improved the overall survival (OS) rate for pediatric CNS tumors, the prognoses for certain entities remain dismal. This chapter will focus on a rare type of pediatric CNS tumor called atypical teratoid rhabdoid tumor (ATRT), delineating current state of knowledge as well as recent advancements in clinical management.

2. Epidemiology and clinical presentation

ATRT is a rare, clinically aggressive CNS tumor that primarily affects very young children but can occur in older children and adults. ATRTs are classified as grade 4 embryonal tumors by the World Health Organization (WHO). ATRT was first defined as an entity in the 1980s (Biggs et al., 1987) but was not recognized as a separate entity by the WHO until 2000 (Kleihues et al., 2002). Prior to this entity being formally recognized,

ATRTs have historically commonly been misdiagnosed as primitive neuroectodermal tumors (PNET, now termed embryonal tumor not otherwise classified/NOS) or medulloblastoma. ATRT has an estimated prevalence of 1 % to 2 % of all pediatric CNS tumors and is the most common malignant CNS tumor in infants (<1 year of age) (Woehrer et al., 2010).

ATRTs comprise approximately 20 % of malignant CNS tumors in children younger than 3 years of age, with 75 % of cases diagnosed in this age group (Packer et al., 2002; Fossey et al., 2017; Hilden et al., 2004). The median age at diagnosis is 16 to 24 months and there is a slight male predominance (Woehrer et al., 2010; Bartelheim et al., 2016; Dufour et al., 2012; Lafay-Cousin et al., 2012). Approximately a third of patients are diagnosed in the first year of life (Fossey et al., 2017). Age at diagnosis had been identified as the strongest independent prognostic factor, with patients younger than 12 months of age having significantly poorer prognosis (Fossey et al., 2017; Bartelheim et al., 2016; Dufour et al., 2012; Frühwald et al., 2020; Quinn et al., 2019; Fischer-Valuck et al., 2017). It is unclear, however, whether age serves as a surrogate of tendency towards avoidance of radiation therapy (RT) in younger patients or there is true difference with age-related tumor biology.

ATRTs may arise in any location in the CNS, with approximately half arising in the posterior fossa (Dho et al., 2015). Location appears to be age-dependent, with supratentorial tumors occurring more commonly with increasing age (Ostrom et al., 2014). Although exceedingly rare, ATRTs can also be seen in adults wherein most tumors are located in the cerebral hemisphere or sellar region (Ostrom et al., 2014; Chan et al., 2018). Primary intraspinal disease is rare and only seen in 1 % to 2 % of cases. Up to 30 % of patients can have CNS metastases or disseminated disease at presentation (Oka & Scheithauer, 1999). Metastatic disease in ATRT has been variably correlated with survival (Hilden et al., 2004; Dufour et al., 2012; Lafay-Cousin et al., 2012; Fischer-Valuck et al., 2017; von Hoff et al., 2011; Buscariollo et al., 2012).

Given its clinically aggressive nature, symptoms typically develop within days to a few weeks. As most tumors are located in the posterior fossa, patients generally present with symptoms of hydrocephalus, namely headaches, nausea and/or vomiting, irritability, lethargy, or increase in head circumference. Ambulatory children may also show signs of gait instability from cerebellar dysfunction. Older children with cortical tumors can present with seizures, lethargy or focal weakness.

2.1 Rhabdoid tumor predisposition syndrome

Malignant rhabdoid tumors (MRTs) were originally described in the kidney and subsequently in extrarenal tissues including the CNS

(Beckwith & Palmer, 1978; Bonnin et al., 1984). Approximately two-thirds of MRTs arise in the CNS where these tumors are coined as ATRTs (Pinto et al., 2018). Up to a third of patients with ATRT have a germline predisposition of developing multiple intra- or extracranial rhabdoid tumors at a very young age, a condition known as Rhabdoid Tumor Predisposition Syndrome (RTPS). RTPS is implicated in up to 80 % of cases of congenital MRTs, where the diagnosis is made prenatally or within the first 28 days of life (Fossey et al., 2017; Frühwald et al., 2021). Median age at presentation is younger for RTPS individuals compared to those with sporadic rhabdoid tumors (5.5 vs 11.5 to 29.5 months) (Nemes et al., 2018, 2021).

In patients with RTPS, more than one tumor can develop simultaneously (synchronous tumors) or new rhabdoid tumors can develop over time (metachronous tumors) (Del Baldo et al., 2021). More than 70 % of children affected with RTPS are diagnosed with synchronous tumors before 12 months of age. The prognostic value of the presence of RTPS is controversial. While one study noted higher risk of death in patients with RTPS (Bruggers et al., 2011), other studies have not confirmed this observation (Bartelheim et al., 2016; Kordes et al., 2014) It is important to note that individuals affected by RTPS are at increased risk of developing other non-rhabdoid tumors such as schwannomas, malignant peripheral nerve sheath tumors (MPNST) and soft tissue sarcomas (Upadhyaya et al., 2018).

RTPS is defined by germline alterations in SMARCB1 or more rarely, SMARCA4, members of the SWI/SNF chromatin-remodeling complex (Del Baldo et al., 2021). RTPS has 2 types, namely RTPS1 and RTPS2, characterized by pathogenic variants in SMARCB1 and SMARCA4, respectively. Both RTPS1 and RTPS2 are inherited in an autosomal dominant fashion. The vast majority of RTPS1 cases are the result of a de novo SMARCB1 mutation (Biegel et al., 2014). While penetrance is high for RTPS1, it is incomplete for RTPS2 (Gastberger et al., 2023). As such, most individuals with SMARCA4-related RTPS inherit the disease-causing variant from an unaffected parent (Hasselblatt et al., 2014).

3. Molecular pathogenesis

3.1 SMARCB1/SMARCA4 inactivation

ATRT was the first primary pediatric CNS tumor in which a candidate tumor suppressor gene (SMARCB1) was identified (Biegel et al., 2014). These

tumors are unique amongst cancer types as they possess a relatively stable genome with very low mutational rates (Lee et al., 2012). Cancer pathogenesis in ATRT is primarily driven by epigenetic dysregulation of the genome resulting from recurrent SMARCB1 alterations. More rarely, mutation and loss of the SMARCA4 gene has been reported whereas no other recurrent alterations have been identified in ATRT (Lanzi et al., 2023).

ATRT was first defined as a separate entity after recognition of recurrent chromosome 22q abnormalities (Rorke et al., 1995, 1996). Abnormalities in the long arm of chromosome 22q were later described as leading to biallelic loss of function of the SWItch/sucrose nonfermentable (SWI/SNF) related, matrix associated, actin dependent regulator of chromatin, subfamily B (SMARCB1) gene, a tumor suppressor gene that encodes BRG1 associated factor 47 (BAF47, also known as integrase interactor [INI1] or human SNF5 [hSNF5]) (Eaton et al., 2011). Much less commonly, biallelic inactivation of SMARCA4 leading to loss of gene expression in the SWI/SNF ATPase Brahma/SWI2-related gene 1 (BRG1) is seen in ATRT patients with wild type SMARCB1 (Schneppenheim et al., 2010). The 2016 WHO Classification of Tumors of the CNS has subsequently defined ATRT by the presence of a genetic alteration in either INI1 (SMARCB1 gene), or rarely, BRG1 protein (SMARCA4 gene) (Louis et al., 2016).

SMARCB1 and SMARCA4 are both core subunits of the SWI/SNF chromatin-remodeling complex (CRC) that plays a crucial role in normal cell differentiation and cell lineage determination. Disruption of the SWI/SNF complex by SMARCB1 loss precludes normal H3K27 acetylation (H3K27Ac) by histone acetylase (HAT) P300 (Alver et al., 2017). In ATRT, loss of H3K27Ac results in repressed chromatin states primarily in active enhancer sites specific to neuronal differentiation programs (Wang et al., 2017; Erkek et al., 2019).

Additionally, ATRTs overexpress the Polycomb Repressive Complex 2 (PRC2) subunit Enhancer of Zeste Homolog 2 (EZH2). Integrated chromatin immunoprecipitation (ChIP) analyses have identified significant overlap between lost enhancers and EZH2-bound chromatin in ATRT (Erkek et al., 2019). SWI/SNF and PRC2 have an antagonistic association that plays an important role in ATRT pathogenesis (Roberts & Biegel, 2009). At repressed neuronal differentiation genes, binding of SWI/SNF to the PRC2 complex is impeded by the transcriptional repressor protein REST. REST then directs PRC2 to repress gene expression at neuronal differentiation sites via deposition of the epigenetic silencing mark H3K27me3 trimethylation of histone H3 on lysine 27. This relationship leads to oncogenic dependency of ATRT cells on

EZH2 enzymatic activity (Knutson et al., 2013). SMARCA4 is necessary for tumorigenesis following SMARCB1 loss, and ChIP data has shown that most SMARCA4-bound targets are also bound by EZH2 (Erkek et al., 2019).

3.2 Molecular subgroups of ATRT

Although genetically homogenous, growing evidence from large-scale DNA methylation and transcriptomic studies have revealed that ATRTs are comprised of three epigenetically distinct and clinically heterogenous subgroups (Johann et al., 2016; Torchia et al., 2016). These molecular subgroups each have unique histopathological, molecular, and clinical characteristics (Upadhyaya et al., 2021). The immune TME differs as well among the different ATRT molecular subtypes (Tran et al., 2023a). A consensus was reached by an international working group to come up with the following nomenclature based on genes overexpressed or upregulated in each subgroup: (1) ATRT-TYR, (2) ATRT-SHH, and (3) ATRT-MYC (Ho et al., 2020) (See Fig. 1).

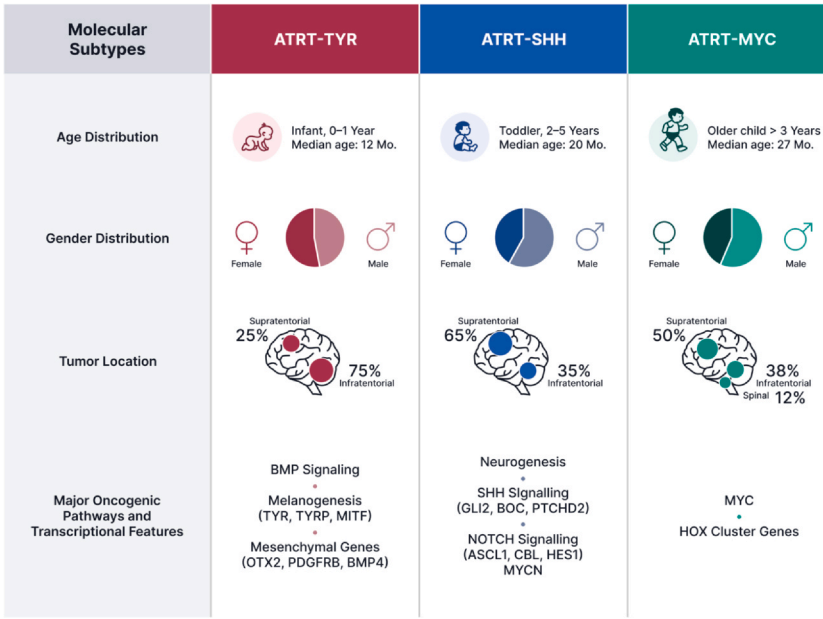

Fig. 1 Molecular subgroups of ATRT.

3.2.1 ATRT-TYR

ATRT-TYR represents approximately 35 % of cases (Johann et al., 2016). The ATRT-TYR subgroup was named after the melanosomal enzyme tyrosinase, which was uniquely highly overexpressed in most ATRT-TYR, but not in the other ATRT subgroups (Hasselblatt et al., 2020). The protein tyrosinase catalyzes the synthesis of melanin in melanocytes and plays an important role in neural tube development (Tief et al., 1996). Other components of the melanosomal pathway are upregulated as well, including tyrosinase-related protein (TYRP) and microphthalmia-associated transcription factor (MITF), a key melanoma oncogene (Johann et al., 2016; Levy et al., 2006). Additional notable major oncogenic pathway and transcriptional features include upregulation of the orthodenticle homeobox 2 (OTX2) gene and the bone morphogenetic protein (BMP) signaling pathway. These tumors have a more mesenchymal expression profile (Johann et al., 2016). ATRT-TYR cases represent the youngest age group, with a median age at diagnosis of 12 months and are mostly (75 %) infratentorial in location (Ho et al., 2020).

3.2.2 ATRT-SHH

ATRT-SHH represents approximately 40 % of cases (Johann et al., 2016). The ATRT-SHH subgroup displays overexpression of the sonic hedgehog (SHH) pathway genes GLI2, protein patched homolog 1 (PTCH1), and brother of CDO (BOC, hedgehog co-receptor). This subgroup is however distinct from SHH medulloblastoma where PTCH and smoothened (SMO) are active drivers. Additionally, this subgroup is characterized by overexpression of Notch signaling pathway genes including the proneural marker achaete-scute homolog 1 (ASCL1). ATRT-SHH can be characterized as a mainly neuronally differentiated subgroup (Torchia et al., 2016). Clinically, ATRT-SHH are intermediate in age between the ATRT-TYR and ATRT-MYC subgroups with a median age at diagnosis of 20 months and can be located both infra- and supratentorially (Johann et al., 2016). It has been suggested that ATRT-SHH can be further divided into 3 molecular subgroups (SHH-1A, SHH-1B, SHH-2), with SHH1-B patients being older with a median age of >3 years (Federico et al., 2022; Tran et al., 2023b).

3.2.3 ATRT-MYC

ATRT-MYC represents approximately 25 % of cases (Johann et al., 2016). The ATRT-MYC subgroup is aptly named due to elevated expression of the MYC oncogene in this subgroup. As opposed to medulloblastoma, no

MYC or MYCN amplifications have been observed among ATRT cases. This subgroup is strikingly characterized by overexpression of several HOX cluster genes. Similar to ATRT-TYR, ATRT-MYC tumors also possess a more mesenchymal expression profile (Johann et al., 2016). ATRT-MYC patients are significantly older than their ATRT-TYR and ATRT-SHH counterparts with a median age of 27 months. ATRT-MYC is most commonly found in ATRT patients diagnosed at age 6 years or older (Frühwald et al., 2020). The majority (50 %) of ATRT-MYC tumors are supratentorial in location. Spinal tumors are uniquely seen in this subgroup and comprise 12 % of ATRT-MYC cases (Ho et al., 2020).

3.3 Impact of molecular subgroups on prognosis

While the ATRT-TYR subgroup has been largely associated with non-metastatic disease and better overall survival (Frühwald et al., 2020; Upadhyaya et al., 2021), the prognostic value of molecular subgroups remains unclear. Data from St. Jude Children's Research Hospital revealed inferior outcomes for the ATRT-SHH subgroup, owing largely to increased risk of metastasis (Upadhyaya et al., 2021). Federico et al., however, reported better outcomes for older patients with ATRT-SHH, belonging to the SHH-1B subgroup (Federico et al., 2022). The St. Jude group has since published their data that failed to show any prognostic significance among ATRT-SHH subgroups in their cohort (Tran et al., 2023b). Although numbers were small, findings from the Children's Oncology Group (COG) ACNS0333 study demonstrated 6-month EFS of 100 % for their ATRT-SHH cohort, suggesting a lower risk of early relapse (Reddy et al., 2021).

3.4 Current conventional therapeutic approaches

No current standard treatment approach exists for ATRT. Intensive regimens following maximal safe resection that utilize varying combinations of high-dose systemic chemotherapy, intrathecal or intraventricular chemotherapy, and radiation have improved the survival for some patients. Even with contemporary multimodal therapy, overall prognosis for ATRT patients still remains dismal, with median survival ranging from 10 to 20 months and 5-year OS of 28 % to 34 % (Fossey et al., 2017; Frühwald et al., 2020; Quinn et al., 2019; Fischer-Valuck et al., 2017; Ma et al., 2020). In North America, treatment strategies have evolved from conventional chemotherapy historically toward an aggressive multimodal strategy incorporating high dose chemotherapy with autologous stem cell rescue (HDCASCR) as a radiation-sparing/radiation-deferring strategy.

ATRT patients treated on historical "baby tumor" prospective trials reported rapid progression and dismal outcomes. In North America, the majority of ATRT patients enrolled on the COG (then Children's Cancer Group and Pediatric Oncology Group) CCG9921 and POG9233/34 trials progressed within a year of diagnosis (Geyer et al., 2005; Strother et al., 2013). For the 64 ATRT patients enrolled on both trials, the 24-month event free survival (EFS) was only 6.4 % (Reddy et al., 2020). In Europe, similar results were seen with ATRT patients treated on German HIT CNS tumor protocols that utilized conventional chemotherapy with or without RT, with 3-year EFS and OS rates of only 13 % and 22 %, respectively (von Hoff et al., 2011).

To date, there have only been three prospective upfront clinical trials designed specifically for ATRT. Until recently, the majority of ATRT patients have been enrolled in trials alongside other infant embryonal tumors.

3.4.1 EU-RHAB

Although not a therapeutic study, the European registry for rhabdoid tumors (EU-RHAB) prospectively collected outcomes for uniformly treated ATRT patients across several European countries. In an earlier publication, EU-RHAB published their outcomes for 31 ATRT patients uniformly treated with the Rhabdoid 2007 treatment schedule (Bartelheim et al., 2016). Diagnosis was centrally confirmed by negative INI1 staining and typical neuropathological features. Features of the Rhabdoid 2007 protocol included use of anthracyclines, intraventricular chemotherapy and early initiation of RT.

Rhabdoid 2007 included 9 total courses of postoperative chemotherapy consisting of alternating courses of vincristine/cyclophosphamide/doxorubicin (VCD x 5 cycles) and ifosfamide/carboplatin/etoposide (ICE x 4 cycles). Intraventricular methotrexate (MTX) or triple chemotherapy (MTX, cytarabine, hydrocortisone) was administered until start of RT. Craniospinal irradiation (CSI) with 24 Gy was reserved for patients age ≥3 years with metastatic disease. Following completion of chemotherapy, recommended maintenance therapy consisted of 8 alternating cycles of trofosfamide/idarubicin (TI) and trofosfamide/etoposide (TE). Eight patients received HDCASCR per treating physician's discretion, 23 received RT, and 17 continued on to maintenance therapy.

6-year EFS and OS were 45 % and 46 %, respectively. The majority of patients experiencing treatment failure (9 of 16) progressed on therapy. Toxicities were significant but manageable. Age ≥3 years at diagnosis demonstrated prognostic OS benefit. Seven of 8 ATRT patients age 3 years and older at diagnosis are long-term survivors. Achievement of complete

remission (CR) status was also of prognostic benefit whereas presence of metastases at diagnosis or germline mutations did not influence OS in the EU-RHAB cohort (Bartelheim et al., 2016). Updated results from the EU-RHAB registry in a larger cohort of 143 evaluable ATRT patients reported 5-year EFS and OS rates of 30.5 % and 34.7 %, respectively (Frühwald et al., 2020). To date, the EU-RHAB Rhabdoid 2007 cohort represents the largest cohort of consistently treated ATRT patients.

3.4.2 DFCI-ATRT

Later efforts to intensify chemotherapy included use of the intensified arm of the Intergroup Rhabdomyosarcoma (IRS)-III study which later led to the first prospective trial designed specifically for ATRT patients by the Dana-Farber Cancer Institute (DFCI) group. Weinblatt and Kochen from Cornell were the first to report the utility of this regimen in a patient with a CNS rhabdoid tumor (Weinblatt & Kochen, 1992). Olson et al. from Ohio State University subsequently published an additional 3 cases successfully treated similarly with IRS-III (Olson et al., 1995). This approach seemed rational given that ATRT was thought to be similar to parameningeal rhabdomyosarcomas. Additionally, the IRS-III regimen was easily adaptable to radiation and the addition of triple intrathecal chemotherapy (Ginn & Gajjar, 2012). The DFCI group themselves reported on the efficacy of this regimen in 3 of 4 ATRT patients (Chi et al., 2009).

Based on the above 8 patients, the DFCI group implemented a multi-institutional phase 2 clinical trial using a modified version of the IRS-III backbone. Modifications in the DFCI-ATRT trial (NCT00084838) included focal stereotactic radiation for patients younger than age 3 years, substitution of dacarbazine with temozolomide, and addition of dexrazoxane for cardioprotection against higher cumulative doses of doxorubicin. Radiation was administered after the initial 6 weeks of induction chemotherapy. Patients age 3 years and older with metastatic disease received CSI. Although numbers were small (N = 20), the above intensive multimodality regimen resulted in significant improvement in 2-year EFS and OS (53 % and 70 %, respectively) compared to historical controls. Univariate analyses revealed tumor location as prognostically significant whereas metastatic status and age at diagnosis were not statistically significant. Significant toxicities were seen in 4 of the 25 study patients which included one toxic death from sepsis (Chi et al., 2009).

Most recently, long-term outcomes from a cohort of 60 patients from 3 large centers (Boston Children's Hospital, Sydney Children's Hospital,

Children's Hospital of Philadelphia/CHOP) treated with IRS-III based chemotherapy regimens have been reported (Desai et al., 2024). Treatment by the CHOP group varied somewhat and incorporated moderately delayed RT with concurrent temozolomide post 6 induction cycles. For the entire cohort, 5- and 10-year EFS were both 30 %. Five- and 10-year OS were 38 % and 45 %, respectively. It was notable that none of the patients with metastatic disease were long-term survivors. Based on the above findings, the authors suggest a possible continued role of IRS-III based strategies for ATRT patients but only those with localized disease.

3.5 Head Start trials

The Head Start (HS) series of trials represented the earliest efforts to study the role of high-dose chemotherapy to avoid or defer RT in very young children (<3 years of age) with brain tumors. In the HS II trial, patients received five cycles of induction chemotherapy comprised of cisplatin, etoposide, cyclophosphamide and vincristine with the addition of high-dose methotrexate. This was followed by a single course of HDCASCR with a preparative regimen of carboplatin, thiotepa and etoposide. Focal RT was reserved for patients with evidence of residual disease or positive CSF cytology after completion of induction therapy. Three of 6 ATRT patients had no evidence of disease at 12, 34, and 46 months from diagnosis. Three-year EFS was 43 %. In the first iteration of the Head Start (HS I), systemic high dose methotrexate was not included and all 6 patients with ATRT died of disease, suggesting a role for high dose methotrexate in the treatment of ATRT. Three-year EFS and OS for patients treated on both Head Start I and II trials combined were 23 % (Gardner et al., 2008).

Nineteen ATRT children were treated on the successor HS III study. Modifications made in HS III included administration of high-dose methotrexate in only 3 of 5 induction cycles and its replacement with temozolomide in cycles 2 and 4. The 3-year EFS and OS were 21 % and 26 %, respectively (Zaky et al., 2014). Comparing the first three HS trials, HS II appeared to have the best outcomes. Possible explanations for the inferior outcomes noted in the HS III trial include a higher toxic death rate (5 of 19) and lower rate of completion during induction (4 of 19) as well as lower cumulative methotrexate doses. Results from the recently completed Head Start 4 trial which randomized high risk medulloblastoma and other embryonal tumors including ATRT to receive single (carboplatin/thiotepa/etoposide) versus triple tandem (carboplatin/thiotepa) HDCASR are forthcoming.

3.6 St. Jude trials

The SJYC07 trial included 55 infants (<36 months of age) with ATRT that were stratified into intermediate or high risk based on the absence or presence of metastatic disease. ATRT infants with intermediate risk disease received 4-drug multi-agent induction chemotherapy x 4 cycles followed by focal RT and oral maintenance chemotherapy x 24 weeks. High risk ATRT infants received additional vinblastine in induction followed by 2 cycles of consolidation with cyclophosphamide and topotecan before moving on to maintenance oral chemotherapy. Optional CSI was offered to patients who were ≥36 months at end of induction. Five-year progression free survival (PFS) and OS for intermediate risk patients were 31.4 % and 43.9 %, respectively. Regrettably, 5-year PFS and OS for those with high-risk disease were 0 % (Upadhyaya et al., 2021). Although RTPS was associated with metastatic status at diagnosis, germline predisposition was not associated with adverse prognosis in the SJYC07 cohort.

The SJMB03 trial had 22 ATRT trial participants ≥36 months of age that were stratified into average or high risk based on the absence or presence of metastatic disease and gross residual tumor. Patients were treated with risk-adapted CSI with boost to primary and metastatic sites followed by 4 cycles of multi-agent chemotherapy with peripheral blood stem cell (PBSC) support. For average risk patients, 5-year PFS and OS was encouraging at 72.7 % and 81.8 %, respectively. Outcomes were far less encouraging for the high-risk cohort with 5-year PFS and OS of 18.2 % (Upadhyaya et al., 2021).

Altogether, the St. Jude Children's Research Hospital prospective risk-adapted trials SJYC07 and SHJMB03 demonstrate a role for multimodal therapy in some children with ATRT. Very good outcomes were seen in children aged ≥3 years with M0 disease after maximal safe resection and postoperative CSI followed by adjuvant consolidation chemotherapy. A subset of children <3 years of age with M0 disease achieved long-term survival without use of HDCASCR.

3.7 ACNS0333

The Children's Oncology Group ACNS0333 trial is the largest prospective therapeutic trial to date specifically for ATRT. ACNS033 was built on the chemotherapy backbone of its predecessor CCG99703 pilot study of intensive chemotherapy with PBSC support for infant malignant brain tumors. Though the number of ATRT patients enrolled on the CCG99703

study were small, data suggested improved survival outcomes compared to CCG9921 (Reddy, 2003). Four of 8 ATRT patients were long term survivors, with a 5-year EFS of 37.5 % (Cohen et al., 2015). Study patients enrolled on ACNS0333 received two cycles of intensive multi-agent chemotherapy with the addition of high dose methotrexate followed by triple tandem HDCASCR with carboplatin and thiotepa and involved field RT (IFRT). Timing of RT was based on patient age and disease location and extent, with younger patients or those with metastatic disease receiving RT after completion of consolidation therapy.

Of 65 evaluable patients enrolled on ACNS0333, 4-year PFS and OS were 37 % and 43 %, respectively. Thirty four of 40 patients who received RT had focal RT only. Patients with no evidence of disease (NED) at the start of radiation had a 4-year OS of 79 % (Alva et al., 2023). About a third of patients, however, had disease recurrence on treatment, with a cumulative incidence of relapse (CIR) of 22 % and 41 % at 6 and 12 months, respectively (Reddy et al., 2021). Nonetheless, survival outcomes from this trial represented a dramatic improvement in survival for children with ATRT compared to historical cohorts where the 4-year EFS was 6.4 %.

Analysis of prognostic variables failed to show any difference in survival by age group (<6 months, 6 to 11 months, 12–35 months) or metastatic status at diagnosis (Reddy et al., 2020). There was a trend towards lower cumulative risk of relapse with infratentorial location (Reddy et al., 2021). ACNS0333 enrolled a lower-than-expected percentage (17 %) of RTPS patients possibly owing to exclusion of patients with synchronous tumors. Although not statistically significant owing to small numbers, it was notable that only 2 of 10 patients with germline mutations survived beyond 2 years.

Main toxicities from the ACNS0333 regimen included myelosuppression and infectious complications. There were 4 treatment related deaths, namely 1 patient died from sepsis during induction therapy, 1 died from pulmonary fibrosis, and 2 succumbed from CNS necrosis. Of note, the study was amended to lengthen the consolidation cycles from 21 to 28 days due to an unexplained fatal pulmonary toxicity as noted above, with no further cases following this amendment (Reddy et al., 2020).

3.8 Prognostic impact of specific treatment modalities for ATRT

3.8.1 Impact of extent of resection

All but one of the above conducted clinical trials failed to show an impact of extent of resection on ATRT survival outcomes. The DFCI-ATRT

trial demonstrated improved PFS and OS for patients who achieved a GTR on univariate analysis. In the DFCI cohort, all patients with NED had a GTR and the 2-year OS for those who achieved a GTR was 91 % (Chi et al., 2009). Similarly, a prior publication that looked at retrospective data from patients on the ATRT registry showed improved EFS for patients who had a GTR (14 months vs. 9.25 months). Based on this, the authors recommended an aggressive surgical approach including second-look surgery when possible to achieve a GTR (Hilden et al., 2004). In the ACNS033 study, only 6 patients underwent second-look surgery after induction chemotherapy and as such, the impact of second-look surgery could not be evaluated (Reddy et al., 2020). Experience from the Canadian Brain Tumor Consortium likewise reported improved survival outcomes after GTR (2-year OS of 60 % vs 21.7 %) (Lafay-Cousin et al., 2012).

Several recent meta-analyses have shown conflicting results on the impact of extent of surgical resection on ATRT outcomes. In a recent meta-analysis by Gupta et al., there was no difference in OS based on extent of resection on univariate or multivariate analysis (Gupta et al., 2024). Conversely, in a prior systematic review by Egiz et al. of ATRT cases confirmed by alterations in INI1 or BRG1, there was a significant survival advantage with GTR on multivariate analysis (Egiz et al., 2022). Yang et al. also found that GTR was associated with better PFS and OS on multivariate analysis (Yang et al., 2020). Pooled analysis by Ma et al. similarly found GTR as an independent positive prognostic factor after adjusting for age and sex (Ma et al., 2020). Two separate meta-analyses specifically looking at metastatic ATRT cases also found variable impact of GTR on survival outcomes (Aridgides et al., 2023; Underiner et al., 2020).

3.8.2 Impact of radiation therapy (RT)

Although the timing, dose and field of RT prescribed by each regimen varies, RT overall appears to have a positive impact on survival for patients with ATRT. In the EU-RHAB Rhabdoid 2007 cohort, RT significantly impacted OS, with 6-year OS of 66 % compared to only 10 % for those not receiving RT (Bartelheim et al., 2016). A separate retrospective analysis of combined cohorts from the EU-RHAB and observational arms of the German HIT/HIT-SKK and AT/RT-ZNS studies yielded similar results and showed that RT was an independent prognostic factor for both PFS and OS on multivariate analysis (Frisch et al., 2024).

Data from the St. Jude group also supports the use of upfront RT. Notably, the only 2 long-term survivors in their historical younger patient

(<3 years of age) cohort both received upfront RT whereas the only patient in their older cohort who died did not receive upfront RT (Tekautz et al., 2005). Of 42 patients in the ATRT registry, 13 patients (31 %) received RT as part of upfront therapy. Nine children received focal RT while 4 were treated with CSI plus a boost to the tumor bed. Median survival for patients receiving RT was longer at 48 months compared to 16.75 months for the entire ATRT registry cohort. Of the 14 long-term survivors in the registry, half received RT as part of upfront therapy (Hilden et al., 2004). Conversely, reported outcomes from the Canadian Brain Tumor Consortium did not demonstrate a survival benefit with upfront radiation (Lafay-Cousin et al., 2012).

Patients treated on the Head Start I and III trials where there was no radiation therapy had dismal prognoses (Gardner et al., 2008). Most of the patients, however, progressed early during treatment, which suggested that other factors such as de-intensified systemic chemotherapy adversely impacted outcomes (Zaky et al., 2014). Although numbers were small, ATRT patients treated on Head Start II which incorporated high dose methotrexate in all induction cycles fared better, with 3 of 6 patients alive with no evidence of disease at time of study publication (Gardner et al., 2008).

In ACNS0333, the order of consolidation HDCASR and RT was based on patient age, tumor location and extent of disease. For 48 of 65 patients who proceeded with protocol therapy after induction chemotherapy, the sequence of RT and HCASR did not affect survival outcomes. Four-year OS was 49 % for RT before HDCASR versus 48 % for HDCASR before RT. Important to note, however, is that 50 % (6 of 12) of patients who received RT after HDCASR received CSI whereas none of those who received RT before consolidation received CSI (Upadhyaya, 2020). Although there was no difference in clinical outcomes based on the order of radiation and HDCASR, increased risk of neurotoxicity was noted when RT was administered between induction and HDCASR (Alva et al., 2023). Planned future trials using this backbone should therefore administer RT after HDCASR.

Several recent meta-analyses also demonstrate the positive impact of RT on survival in ATRT patients. In the meta-analysis by Yang et al., RT was a significant favorable prognostic factor for both PFS and OS in ATRT patients < 3 years of age whereas early (i.e. within 2 months of diagnosis) RT significantly improved OS for patients ≥3 years of age. Timing of RT did not affect survival outcomes for younger patients (Yang et al., 2020). Ma et al. similarly found that RT was an independent positive prognostic factor after

adjusting for age and sex (Ma et al., 2020). In a meta-analysis by Underiner et al. looking specifically at metastatic ATRT patients, RT was found to significantly improve survival on multivariate analysis (Underiner et al., 2020).

3.8.3 Impact of high dose chemotherapy with autologous stem cell rescue (HDCASCR)

HDCASCR has been associated with improved survival in several ATRT studies including the landmark COG ACNS0333 study (Lafay-Cousin et al., 2012; Reddy et al., 2020; Zaky et al., 2014; Nicolaides et al., 2010; Sung et al., 2016; Finkelstein-Shechter et al., 2010; Slavc et al., 2014). ACNS0333 represents the largest conducted prospective clinical trial for patients with ATRT and utilized triple tandem HDCASCR in addition to RT after induction therapy. The Canadian Brain Tumor Consortium also reported better outcomes (2-year OS 47.9 % vs 12.1 %) after HDCASCR in their cohort (Lafay-Cousin et al., 2012). Although an earlier report from the EU-RHAB cohort suggested possible benefit from HDCASCR in select ATRT patients with localized disease (Benesch et al., 2014), updated analysis from the EU-RHAB cohort failed to demonstrate significant improvement in survival among 34 patients who received HDCASCR (Frühwald et al., 2020).

Only about half of the recently published meta-analyses looked at the prognostic impact of HDCASCR on ATRT outcomes. Ma et al. showed that HDCASCR was an independent positive prognostic factor after adjusting for age and sex (Ma et al., 2020). Yang et al. found that HDCASCR improved both PFS and OS on multivariate analysis but only for patients aged <3 years (Yang et al., 2020). Specifically looking at metastatic ATRT cases, Underiner et al. noted HDCASCR to have the most substantial effect on survival outcomes on multivariate analysis. In their meta-analysis, 3-year OS was 60 % for metastatic ATRT patients who received HDCASR compared to 9 % for those who did not (Underiner et al., 2020). While Arigides et al. noted a trend towards survival advantage of metastatic patients that received HDCASCR, this was statistically significant only on univariate but not on multivariate analysis (Aridgides et al., 2023).

Randomized clinical trials to determine the advantage of HDCASCR over conventional chemotherapy and radiotherapy-based approaches are much needed. The European Society of Paediatric Oncology (SIOPE) has recently launched SIOPE ATRT101, an international prospective umbrella trial for pediatric ATRT that includes a randomized phase 3 study evaluating the non-inferiority of 3 courses of HDCASR compared to focal RT as consolidation therapy in children between 12 and 35 months of age.

Table 1 Published results from prospective studies for ATRT.

Protocol	Number of patients (N)	Chemotherapy regimen	Upfront RT (N)	HDCASR (N)	IT/intraventricular chemo	Outcomes
EU-RHAB Rhabdoid 2007 Bartelheim et al. (2016)	143	Induction: VCR, CPM, DOX alternating with IFOS, CPM, VP-16 × 9 total cycles Maintenance: TFF, IDA alternating with TFF, VP-16 × 8 cycles	81	34	Yes	5-yr EFS: 30.5 % + /− 4.2 % 5-yr OS: 34.7 % + /− 4.5 %
DFCI-ATRT Frühwald et al. (2020)	20	Induction: VCR, CDDP, DOX, CPM, VP-16, DACT × 18 weeks Maintenance: TMZ, DACT, VCR, DOX, CPM × 24 weeks Continuation Therapy: VCR, DOX^{+}, CPM, DACT 9 weeks	15 (11 focal, 4 CSI)	NA	Yes	2-yr PFS: 53% + /− 13% 2-yr OS: 70% + /− 10%
Head Start (HS) I/II Desai et al. (2024)	13 (HS I: 6, HS II: 7)	Induction: CDDP, VP-16, CPM, HD MTX*, VCR^ × 5 cycles HDCASR Consolidation: CBP, TEPA, VP-16 × 1 cycle	1	7	No	3-yr EFS and OS: 23 % + /− 11 % HS II 3-yr EFS: 43 % + /− 9 %

(continued)

Table 1 Published results from prospective studies for ATRT. (*cont'd*)

Protocol	Number of patients (N)	Chemotherapy regimen	Upfront RT (N)	HDCASR (N)	IT/intraventricular chemo	Outcomes
Head Start III Gardner et al. (2008)	19	Induction Cycles 1, 3, 5: CDDP, VCR, VP-16, CPM, HD MTX Induction Cycles 2, 4: TMZ, VP-16, VCR, CPM HDCASCR: Consolidation: CBP, TEPA, VP-16 × 1 cycle	0	3	No	3-yr EFS: 21 % + /− 9 % 3-yr OS: 26 % + /− 10 %
SJYC07 Torchia et al. (2016)	55	IR Induction: HD MTX, VCR, CPM, CDDP, (VBL for HR only) × 4 cycles Consolidation (HR only): CPM, TOPO × 2 cycles Maintenance: PO CPM, TOPO alternating with PO VP-16 × 6 cycles	34 (focal, for IR only)	NA	No	IR 5-yr PFS: 31.4 % + /− 9.2 % 5-yr OS: 43.9 % + /−9.5 % HR 5-yr PFS and OS: 0 %

SMB03 Torchia et al. (2016)	22	HDCASR: CDDP, VCR, CPM x 4 cycles	22	22	No	AR 5-yr PFS: 72.7 % + /− 12.7 % 5-yr OS: 81.8 % + /− 11 % HR 5-yr PFS and OS: 18.2 % + /− 9.5 %
ACNS0333 Cohen et al., (2015)	65	Induction: HD MTX, VCR, VP-16, CPM, CDDP × 2 cycles HDCASR Consolidation: CBP, TEPA × 3 cycles	40 (34 focal, 6 CSI)	42 (20 pre-RT, 22 post-RT)	No	4-yr EFS: 37 % 4-yrOS: 43 %

Abbreviations: AR, average risk; ATRT, atypical teratoid rhabdoid tumor; CDDP, cisplatin; CPM, cyclophosphamide; CSI, craniospinal irradiation; DACT, dactinomycin; DOX, doxorubicin; EFS, event-free survival; IDA, idarubicin; IT, intrathecal; HDCASR, high dose chemotherapy with autologous stem cell rescue; HD MTX, high-dose methotrexate; HR, high risk; IFOS, ifosfamide; IR, intermediate risk; OS, overall survival; PFS, progression-free survival; RT, radiation therapy; TFF, trofosfamide; TMZ, temozolomide; TOPO, topotecan; VP-16, etoposide;

* Head Start II only

^ Cycles 1-3 only

+ Only if < 18 Gy RT thoracic spine/mediastinum

Table 2 Active clinical therapeutic trials for ATRT.

NCT number	Study title	Conditions	Available regions
NCT06622941	Study to ONO-4538 in Patients with Rhabdoid Tumor	Rhabdoid Tumor including ATRT	Japan
NCT05286801	Tiragolumab and Atezolizumab for the Treatment of Relapsed or Refractory SMARCB1 or SMARCA4 Deficient Tumors	Rhabdoid Tumor including ATRT, Epithelioid Sarcoma, Renal Medullary Carcinoma	USA, Australia, Canada
NCT05407441	Tazemetostat+Nivo/Ipi in INI1-Neg/SMARCA4-Def Tumors	ATRT, MRT, RTK, Chordoma, Epithelioid Sarcoma, INI1 (SMARCB1)- or SMARCA4-deficient Primary CNS Tumors	USA
NCT06193759	Immunotherapy for Malignant Pediatric Brain Tumors Employing Adoptive Cellular Therapy (IMPACT)	ATRT, ETMR, Medulloblastoma, Pineoblastoma, other CNS Embryonal Tumors	USA
NCT04416568	Study of Nivolumab and Ipilimumab in Children and Young Adults with INI-1 Negative Cancers	ATRT, MRT including RTK, Chordoma (Poorly Differentiated or De-differentiated), Epithelioid Sarcoma, Other INI1-Negative or SMARCA4-deficient Malignant Tumors (with PI Approval)	USA
NCT05835687	Loc3CAR: Locoregional Delivery of B7-H3-CAR T Cells for Pediatric Patients with Primary CNS Tumors	ATRT, High Grade Glioma including Glioblastoma, DMG, Medulloblastoma, Ependymoma, Other CNS Tumors	USA

NCT02905110	Methotrexate and Etoposide Infusions into the Fourth Ventricle in Children with Recurrent Posterior Fossa Brain Tumors	Recurrent CNS Tumors	USA
NCT04185038	Study of B7-H3-specific CAR T Cell Locoregional Immunotherapy for Diffuse Intrinsic Pontine Glioma/ Diffuse Midline Glioma and Recurrent or Refractory Pediatric Central Nervous System Tumors	ATRT, DMG/DIPG, Medulloblastoma, Pineoblastoma, PNET, Ependymoma, Glioma, Choroid Plexus Carcinoma, Other CNS Tumors	USA
NCT04099797	C7R-GD2. CAR T Cells for Patients with GD2-expressing Brain Tumors (GAIL-B)	Embryonal CNS Tumors including ATRT, DIPG, ETMR, High Grade Glioma	USA
NCT04715191	Interleukin-15 and-21 Armored Glypican-3-specific Chimeric Antigen Receptor Expressed in T Cells for Pediatric Solid Tumors	Rhabdoid Tumors including ATRT, Rhabdomyosarcoma, Wilms Tumor, Yolk Sac Tumor, Liposarcoma, Liver CA	USA
NCT04377932	Interleukin-15 Armored Glypican 3-specific Chimeric Antigen Receptor Expressed in T Cells for Pediatric Solid Tumors	Rhabdoid Tumors including ATRT, Rhabdomyosarcoma, Wilms Tumor, Yolk Sac Tumor, Liposarcoma, Liver CA	USA
NCT04541082	Phase I Study of Oral ONC206 in Recurrent and Rare Primary Central Nervous System Neoplasms	ATRT, Anaplastic Astrocytoma/Oligodendroglioma/ PXA, Diffuse Astrocytoma, DMG, Ependymoma, Glioblastoma, Medulloblastoma, PNET, Pineal Tumor, Anaplastic/Atypical Meningioma, Choroid Plexus Neoplasms,	USA
NCT05985161	A Study of Selinexor in People with Wilms Tumor and Other Solid Tumors		USA

(continued)

Table 2 Active clinical therapeutic trials for ATRT. (*cont'd*)

NCT number	Study title	Conditions	Available regions
		Rhabdoid Tumors including ATRT, Wilms Tumor/Nephroblastoma, MPNST, Other Solid Tumors	
NCT03911388	HSV G207 in Children with Recurrent or Refractor Cerebellar Brain Tumors	Other Primary Cerebellar Neoplasms including ATRT, Astrocytoma, PNET, Medulloblastoma	USA
NCT05103631	Interleukin-15 Armored Glypican 3-specific Chimeric Antigen Receptor Expressed in Autologous T Cells for Solid Tumors	MRT, Emryonal Sarcoma of the Liver, Liposarcoma, Liver Cell Carcinoma, Rhabdomyosarcoma, Wilms Tumor, Yolk Sac Tumor, Other Solid Tumor	USA
NCT04897321	B7-H3-specific Chimeric Antigen Receptor Autologous T-Cell Therapy for Pediatric Patients with Solid Tumors (3CAR)	Rhabdoid Tumor including ATRT, Adrenocortical CA, Clear Cell Sarcoma, DSRCT, Ewing sarcoma, Germ Cell Tumor, Hepatoblastoma, MPNST, Melanoma, Neuroblastoma, Osteosarcoma, Rhabdomyosarcoma, Soft Tissue Sarcoma, Wilms Tumor, Other Pediatric Solid Tumor	USA
NCT03618381	EGFR806 CAR T Cell Immunotherapy for Recurrent/Refractory Solid Tumors in Children and Young Adults	Rhabdoid Tumor including ATRT, Clear Cell Sarcoma, DSRCT, Ewing sarcoma, Germ Cell Tumor, Hepatoblastoma, MPNST, Neuroblastoma, Osteosarcoma, Retinoblastoma, Rhabdomyosarcoma,	USA

		Soft Tissue Sarcoma, Synovial Sarcoma, Wilms Tumor, Other Pediatric Solid Tumor	
NCT01356290	Antiangiogenic Therapy for Children with Recurrent Medulloblastoma, Ependymoma and ATRT	ATRT, Ependymoma, Medulloblastoma	USA, Austria, Czech Republic, Denmark, France, Norway, Spain, Sweden,
NCT05135975	A Study of Cabozantinib as a Maintenance Agent to Prevent Progression or Recurrence in High-Risk Pediatric Solid Tumors	Neuroblastoma, Sarcoma, Other Solid Tumor	USA

Abbreviations: ATRT, atypical teratoid rhabdoid tumor; CAR, chimeric antigen receptor; CNS, central nervous system; DIPG, diffuse intrinsic pontine glioma; DMG, diffuse midline glioma; DSRCT, desmoplastic small round cell tumor; ETMR, embryonal tumor with multilayered rosettes; HSV, herpes simplex virus; MPNST, malignant peripheral nerve sheath tumor; MRT, malignant rhabdoid tumor; PI, principal investigator; PNET, primitive neuroectodermal tumor; RTK, rhabdoid tumor of the kidney; USA, United States of America

List of clinical trials obtained from www.clinicaltrials.gov website using search words "ATRT" and "rhabdoid".

3.8.4 Impact of intrathecal/intraventricular chemotherapy

Intrathecal/intraventricular (IT) chemotherapy has been used as an adjunct to systemic chemotherapy for patients with ATRT. IRS-III based strategies in particular incorporate IT chemotherapy into its backbone. Historical meta-analysis by Athale et al. has previously linked intrathecal chemotherapy with improved survival in patients who did not undergo RT (Athale et al., 2009). Only 2 contemporary meta-analyses looked at the prognostic impact of IT chemotherapy on ATRT outcomes. In both studies, IT chemotherapy was independently associated with improved survival (Ma et al., 2020; Underiner et al., 2020).

3.9 Summary recommendations based on prospective upfront ATRT clinical trials

Although the aforementioned trials have led to improved outcomes for patients with ATRT, they incorporated varying combinations of conventional chemotherapy, RT, HDCASCR, and IT chemotherapy. Therefore, there remains no established standard of care for newly diagnosed patients with ATRT. Given similar patient characteristics and outcomes among patients on the ACNS0333 and DFCI-ATRT studies, we recommend treatment per either ACNS0333 or the DFCI-ATRT backbone for ATRT patients <3 years of age. More recent data using IRS-III based strategies, however, cautions against its use in patients with metastatic disease. SJMB03 should also be considered for patients age 3 years or older with localized disease who have achieved a GTR.

Table 1 lists a summary of key findings from completed upfront ATRT clinical trials.

Table 2 lists active clinical therapeutic trials for ATRT.

4. Innovative mechanism-driven therapeutics for ATRT

4.1 Chromatin remodeling and histone modification

4.1.1 HDAC inhibition

SWI/SNF histone modifications are critical in ATRT pathogenesis. Histone acetyltransferases and histone deacetylases (HDACs) control the acetylation status of the downstream histone target H3K27 in ATRT (Roberts & Biegel, 2009). The HDAC family is subdivided into class I (HDAC 1, 2, 3 and 8), class II (HDAC 4, 5, 6, 7, 9 and 10), and class IV (HDAC11) based on sequence similarity to yeast deacetylases (Park & Kim, 2020). HDAC1 and HDAC2 are overexpressed in ATRT primary tumors

and cell lines (Frühwald et al., 2016). Histone acetylation therefore serves as an attractive therapeutic target for ATRTs.

ATRT cell proliferation is impaired by a variety of HDAC inhibitors (HDACi) including valproic acid, vorinostat (suberoylanilide hydroxamic acid or SAHA), panobinostat (LBH589), and entinostat (MS-275). Vorinostat, a first-generation pan-HDACi, inhibits HDAC activity by inserting into the active site of the enzyme, resulting in G1 and G2/M cell cycle arrest and p53-independent apoptosis (Xu et al., 2007). Resultant buildup of acetylated histones leads to preferential increased transcription of genes associated with neuronal differentiation or apoptosis (Yin et al., 2007). Kerl et al. reported on the synergistic activity of vorinostat when combined with chemotherapy against MRT cells. Additionally, vorinostat was shown to induce deregulated gene programs associated with cell cycle progression (MYC, RB, stem cell programs) (Kerl et al., 2013). Vorinostat has also been demonstrated to enhance both in vitro and in vivo radiosensitivity of MRT cells (Knipstein et al., 2012; Thiemann et al., 2012). A phase 1 study of vorinostat combined with temozolomide for relapsed/refractory pediatric CNS tumors (NCT01132911) has been completed by the Children's Oncology Group. Although the combination was well tolerated, there was limited clinical activity in a heterogenous group of CNS tumors that included 2 ATRT cases (Hummel et al., 2013).

Panobinostat is another first-generation pan-HDACi considered to have the highest potency compared to other pan-HDACis (Al Shoyaib et al., 2021). In vitro work by Muscat et al. demonstrated that low dose treatment with panobinostat can terminally differentiate MRT cells and inhibit self-renewal (Muscat et al., 2016). Chong et al. showed in an orthotopic ATRT xenograft model that continuous treatment with panobinostat leads to inhibition of tumor growth, improvement in survival, and neuronal differentiation (Chong et al., 2021). A phase 2 study of low dose panobinostat as maintenance therapy for pediatric solid tumors including MRT/ATRT (NCT04897880) was terminated early due to drug supply issues (Wood et al., 2020).

Several second-generation HDACis are now currently being investigated in early phase clinical trials and are expected to provide improved risk-benefit ratio owing to them being class- or isoform-selective (Yang et al., 2019). Entinostat (MS-275), a second-generation selective class I and IV HDACi, has been evaluated in a phase 1 study (ADVL1513) by the Pediatric Early Phase-Clinical Trial Network (PEP-CTN) for pediatric recurrent/refractory solid tumors including CNS tumors (NCT02780804) but failed to show any evidence of single agent activity in a heterogenous cohort of

pediatric solid tumors (Bukowinski et al., 2021). Entinostat, however, has been reported to have poor blood-brain barrier (BBB) penetration, suggesting limitation as a therapeutic candidate for CNS tumors (Hooker et al., 2010). The second-generation CNS penetrant HDACi quisinostat (JNJ-26481585) possesses subnanomolar specificity for class I HDAC isoforms, particularly HDAC1 and HDAC2, which are both highly expressed in ATRT. Quisinostat demonstrated broad in vitro cytotoxicity in a panel of pediatric tumor cell lines including MRT, as well as retarded tumor growth in the majority of solid tumor xenografts tested (Carol et al., 2014). Cascio et al. reported on the radiosensitizing properties of quisinostat in preclinical models of glioblastoma (GBM) (Lo Cascio et al., 2023).

4.1.2 EZH2 inhibition

The antagonistic relationship between the SWI/SNF and PRC2 complexes plays an important role in ATRT pathogenesis via regulation of downstream targets EZH2 and H3K27 (Roberts & Biegel, 2009). This antagonistic relationship leads to oncogenic dependency of ATRT cells on EZH2 enzymatic activity. In mouse models, genetic inactivation of EZH2 has been shown to block tumor formation driven by SMARCB1 loss (Wilson et al., 2010). The EZH2 inhibitor tazemetostat (EZH-102) has been shown to induce apoptosis and differentiation in INI1-negative MRT cell lines. In xenograft-bearing mice, EZH2 inhibition led to dose-dependent regression of MRTs with correlative reduction in intratumoral H3K27me3 and prevention of tumor regrowth after treatment cessation (Knutson et al., 2013). Alimova et al. provided evidence that tazemetostat alters cell cycle progression and significantly impairs tumor growth in ATRT cells as well as potently sensitizes them to RT (Alimova et al., 2013). Klaus et al. found that tazemetostat given before or concomitantly with RT induced robust in vitro antiproliferative activity and reduction in clonogenic potential in ATRT cell lines (Klaus et al., 2017).

Tazemetostat was investigated in a phase 1 pediatric study for relapsed/refractory INI1-negative tumors including ATRT (NCT02601937). Objective responses were seen in 24 % (5 of 21) of ATRT patients (Chi et al., 2022). Tazemetostat was generally well tolerated at doses up to 1200 mg/m^2/dose twice daily (2400 mg/m^2/day). There was a non-statistical trend towards improved objective response rate (ORR) for patients who have received prior RT, suggesting potential synergism between RT and tazemetostat. The phase 2 National Cancer Institute (NCI)-COG Pediatric Molecular Analysis for Therapy Choice (MATCH) APEC1621C

trial for tumors harboring SMARCB1/SMARCA4 or EZH2 alterations including ATRT (NCT03213665) did not meet its primary ORR efficacy endpoint. Although ORR was only 5 % in the entire cohort, 25 % of patients including 1 patient with ATRT experienced durable (≥6 months) prolonged disease control, suggesting a potential effect of tazemetostat for disease stabilization. Tazemetostat in combination with immune checkpoint inhibition using nivolumab and ipilimumab is currently under investigation in a phase I/II setting for pediatric INI1-negative or SMARCA4-deficient tumors (NCT05407441).

GSK126 is another EZH2 inhibitor that has demonstrated in vitro and in vivo preclinical activity either alone or in combination with the bromodomain inhibitor JQ1 against ATRT (Ishi et al., 2022). GlaxoSmithKline, however, has discontinued the development of GSK126 owing to insufficient evidence of clinical activity against hematologic malignancies for which it was developed (Gulati et al., 2018).

4.1.3 Bromodomain and extra-terminal protein (BET) inhibition

ATRT cells express high levels of c-MYC, and chromatin immunoprecipitation (ChIP)-sequencing experiments conducted by Alimova et al. have demonstrated significant enrichment of MYC chromatin occupancy at transcriptional sites in ATRT (Alimova et al., 2019). MYC is a core transcription factor that controls numerous cellular functions, and in the malignant state, aberrant MYC activity drives transcriptional programs that lead to tumor growth, metastasis, chemoresistance and reversal to a stem cell-like state (Dang, 2012). Direct MYC targeting, however, is highly challenging, largely owing to the absence of a clear ligand-binding domain (Delmore et al., 2011). Several compounds have already been developed as alternative strategies to target MYC including bromodomain (BET) inhibitors. Transgenic knockdown of c-MYC effectively restricted in vivo growth and prolonged survival of ATRT patient-derived xenograft (PDX) mouse models, providing a rationale for use of BET inhibitors for ATRT (Alimova et al., 2019).

Recent genome wide ChIP-sequencing analyses also identified high occupancy of H3K27ac in association with BET bromodomain-containing protein 4 (BRD4) at ATRT enhancer elements (Johann et al., 2016). Acetylated histones bind to BRD4 and activate gene transcription. The potent highly selective BET inhibitor JQ1 specifically blocks binding between BRD4 and acetylated histone, resulting in suppression of gene transcription (Popovic & Licht, 2012). Treatment with the potent BET inhibitor JQ1

significantly attenuated c-MYC transcription and MYC-driven stemness programs as well as significantly prolonged survival in orthotopic xenograft mouse models of ATRT (Alimova et al., 2019). Moreno et al. also reported on BRD4 inhibition alone or in combination with CDK9 inhibition resulting in efficient in vitro impairment of cellular proliferation and induction of cytotoxicity in MRT (Moreno et al., 2017).

To date, most adult trials of pan-BET inhibitors have been challenged by their narrow therapeutic index and modest anti-tumor activity as monotherapy (Pearson et al., 2021). The first pediatric trial of BET inhibition with ezobresib (BMS-986158) (Arm 1) and trotabresib (BMS-986378/CC-90010) (Arm 2) (NCT03936465) was recently completed by the Dana-Farber group with forthcoming results.

4.1.4 Other epigenetic therapies

The anti-viral drug ribavirin is structurally similar to the EZH2 inhibitor 3-deazaneplanocin A (DZNep) (De la Cruz-Hernandez et al., 2015). Ribavirin has shown preclinical activity against ATRT cells via down-regulation of EZH2 and potentially impeding eukaryotic initiation factor 4E (eIF4E). Treatment with ribavirin significantly improved survival in an ATRT-MYC B12 orthotopic mouse model (Casaos et al., 2018). Consistent with this finding, recent integrated pharmacogenomic analysis revealed subgroup specific sensitivity of ATRT-MYC cells to the eIF4E inhibitor briciclib (Pauck et al., 2025).

Of the three molecular ATRT subgroups, ATRT-TYR and ATRT-SHH demonstrate global hypomethylation, providing a rationale for the use of hypomethylating agents (HMA) (Johann et al., 2016). The EU-RHAB group reported on clinical outcomes of 22 ATRT patients who received individualized low-dose-decitabine-augmented chemotherapy after relapse or disease progression following upfront Rhabdoid 2007 therapy. In this highly refractory setting, 27.3 % of patients demonstrated radiographic response (including 1 CR), with responders experiencing prolonged time to progression and overall survival. Analysis of methylation data suggested a possible influence of tumor methylation levels on HMA response (Steinbügl et al., 2021).

Curaxin (CBL0137) is a CNS penetrant DNA-binding small molecule that is related to the anti-malarial drug quinacrine (Jin et al., 2018). Curaxin targets spatial genome organization and acts as an epigenetic agent by trapping the Facilitator of Chromatin Transcription (FACT) complex within chromatin, which in turn results in p53 phosphorylation and

suppression of nuclear factor κβ (NF-κβ) (Gasparian et al., 2011). Curaxin has demonstrated in vitro cytotoxicity against ATRT cells and in vivo growth suppression of MRT flank xenografts (Lock et al., 2017). A phase 1/2 trial of curaxin is being evaluated by the PEP-CTN in an ongoing phase 1/2 trial for relapsed/refractory pediatric solid tumors including CNS tumors and lymphoma (PEPN2111, NCT04870944).

4.2 Cell cycle regulation

4.2.1 Aurora A kinase inhibition

The Aurora family of serine/threonine kinases plays a critical role in the regulation of chromosomal segregation and cytokinesis during mitosis. Aurora kinase A (AURKA) and B are expressed in all actively dividing cells, whereas Aurora kinase C expression is largely restricted to dividing germ cells (Nigg, 2001). AURKA plays a critical role in the formation and stability of the mitotic spindle and is highly overexpressed in ATRT cells (Nikonova et al., 2013). Lee et al. were the first to demonstrate that AURKA is a direct downstream target of INI1-mediated repression in MRT cells and that INI1 loss leads to aberrant AURKA overexpression that is required for MRT survival (Lee et al., 2011).

Alisertib (MLN8237) is a selective small molecule reversible inhibitor of AURKA via ATP-competitive binding (Manfredi et al., 2011). Alisertib was evaluated within the NCI-supported Pediatric Preclinical Testing Program (PPTP) which selectively tests 10 to 12 agents or combinations of agents annually in in vitro and in vivo preclinical models of common childhood cancers. Alisertib was initially found to have significant activity against solid tumors, most notably neuroblastoma, and pediatric leukemia xenografts (Carol et al., 2011). Alisertib has also been demonstrated to suppress the activity of pro-proliferative signaling pathways, induce cell death and enhance radiation sensitivity in ATRT cell lines (Venkataraman et al., 2012).

Alisertib was evaluated in a pediatric phase 1 trial by the COG for relapsed/refractory solid tumors (ADVL0812, NCT02444884). Notably, there was a greater frequency of myelosuppression and hand-foot-syndrome than reported in the adult literature with twice daily dosing that was mitigated by once daily higher dosing. The recommended phase 2 dose (RP2D) was 80 mg/m^2/day (Mossé et al., 2012). In the phase 2 COG study of alisertib for recurrent/refractory pediatric solid tumors or leukemia (ADVL0921, NCT01154816), although well tolerated, ORR was only 5 % as a single agent. No response was seen in all 4 patients with ATRT/MRT enrolled on this study (Mossé et al., 2019). Conversely, in an earlier

small pilot study by the St. Jude group for recurrent ATRT, single agent alisertib produced durable disease control in 4 patients, with a median duration of 11 months (Wetmore et al., 2015). Although the phase 2 SJATRT study for recurrent ATRT (NCT02114229) did not meet its predetermined efficacy end point, stable disease (SD) or partial response (PR) was observed in approximately a third of study patients. Neutropenia was the most common side effect noted. One-year PFS and OS were 30 % and 36.7 %, respectively. Treatment responses or PFS did not differ by ATRT molecular subgroup (Upadhyaya et al., 2023).

4.2.2 Cyclin D1 inhibition

Earlier studies have proposed that INI1 loss induces cell cycle proliferation by direct transcriptional activation of cyclin D1 (CCND1) and repression of cyclin-dependent kinase (CDK) inhibitors p16INK4A and p21 (Zhang et al., 2002; Oruetxebarria et al., 2004). Consistent with this theory, Tsikitis et al. demonstrated that INI1 heterozygous mouse models with genetically induced cyclin D1 failed to develop MRT (Tsikitis et al., 2005). More recently, however, Xue et al. showed that SMARCB1 loss in ATRT leads to reduced cyclin D1 expression via upregulation of the microRNA (miRNA) MIR17HG (miR-17–92) gene cluster, which produces miRNAs that target cyclin D1 (Xue et al., 2020). Additionally, ATRT patient tumors were generally RB-proficient and p16-deficient, which has been linked to positive responsiveness to CDK4/6 inhibitors (O'Leary et al., 2016). Functional genomic screening via CRISPR-Cas9 knockout identified CDK4/6 among the most potent drugs against ATRT (Merk et al., 2024). Thus, targeting the cyclin D-CDK4/6-INK4a-Rb axis appears to be a biologically rational treatment strategy for ATRT.

Palbociclib (PD-0332991) is a potent selective inhibitor of CDK4 and CDK6. Katsumi et al. showed that human MRT cell lines were sensitive to palbociclib and that p16 overexpression inversely correlated to growth inhibitory effect from palbociclib (Katsumi et al., 2011). Hashizume et al. found that adjuvant or concurrent use of palbociclib with RT inhibited double-strand DNA (dsDNA) break repair and promoted tumor cell apoptosis in ATRT mouse models (Hashizume et al., 2016). The NCI-COG pediatric MATCH trial Arm I (APEC1621I, NCT03526250) was a phase 1 study of single agent palbociclib for pediatric solid tumors with genomic alterations in the cyclin D-CDK4/6-INK4a-Rb pathway. Although palbociclib was well tolerated in this heavily-pretreated cohort, no objective responses were observed at the study dose of 75 mg/m^2 daily, suggesting that

cyclin D-CDK4/6-INK4a-Rb pathway alteration alone is insufficient to generate a response in pediatric malignancies (Macy et al., 2024). Further evaluation of palbociclib in combination with chemotherapy in pediatric patients with recurrent/refractory solid tumors is underway (NCT03709680).

Ribociclib (LEE001) is another CDK4/6 inhibitor that has displayed preclinical activity in MRT cells (Hua et al., 2024). In vitro screens of a panel of more than 500 cell lines from the Novartis Cancer Cell Line Encyclopedia identified MRT cell lines to be among the most sensitive to ribociclib treatment (Geoerger et al., 2017). In a phase 1 study of ribociclib for pediatric MRT, neuroblastoma, and other solid tumors (NCT01747876), 5 of 32 patients achieved prolonged (≥6 cycles) and included 2 patients with ATRT. Ribociclib demonstrated acceptable safety with a 3-weeks-on/1-week-off dosing schedule and the RP2D was 350 mg/m^2. The most common adverse effect reported was myelosuppression (Geoerger et al., 2017).

Several studies combining ribociclib with other agents in pediatric solid tumors including ATRT are underway. Among these is the ongoing phase 1/2 study evaluating ribociclib in combination with topotecan and temozolomide (TOTEM) for relapsed/refractory neuroblastoma and other pediatric solid tumors (NCT05429502). The above combination had been previously evaluated in Arm A of the phase I/II Access Secured-European Proof-of-Concept Therapeutic Stratification Trial of Molecular Anomalies in Relapsed or Refractory Tumors (AcSé-ESMART) (NCT02813135). No objective responses were seen and only 14.3 % of patients had SD as best response (Bautista et al., 2021).

Abemaciclib is another CDK4/6 inhibitor that is currently being clinically tested in pediatric recurrent/refractory solid tumors (NCT0264460). Compared to palbociclib and ribociclib abemaciclib is more highly bound to plasma proteins and can better penetrate the blood-brain barrier due to its improved lipophilicity (Braal et al., 2021). Abemaciclib significantly prolonged survival of orthotopic mouse xenograft models of ATRT-MYC and ATRT-SHH (Merk et al., 2024). Ding et al. tested TG02, a multi-CDK (CDK 1, 2, 5, 7 and 9) inhibitor in ATRT cells and observed that TG02 significantly impaired in vitro cell proliferation by limiting clonogenicity and inducing apoptosis. Additionally, TG02 acted as a potent radiosensitizer and synergized with cisplatin against ATRT cells (Ding et al., 2021).

4.2.3 MDM2 inhibition

Mouse double minute 2 homolog (MDM2) is a proto-oncogene that plays a crucial role as the primary negative regulatory factor of the tumor

suppressor gene p53. MDM2 encodes a nuclear-localized E3 ubiquitin protein ligase that marks p53 for proteasomal degradation (Hou et al., 2019). Using large scale RNAi, CRISPR-Cas9, and small molecule libraries, Howard et al. identified MDM2 (also MDM4) as a therapeutic vulnerability in MRT cell lines (Howard et al., 2019). Alimova et al. found increased MDM2 expression levels in ATRT patient samples. Additionally, ATRT cells demonstrated in vitro and in vivo sensitivity as well as increased radiosensitivity in response to MDM2 inhibition (Alimova et al., 2022). Most recently, high throughput drug screening of 13 different ATRT cell lines by Pauck et al. revealed sensitivity to MDM2 inhibitors which is in line with earlier reports (Pauck et al., 2025).

The St. Jude group opened the phase 1 iSTAR trial of the orally bioavailable MDM2 inhibitor idasanutlin (RG7388) combined with the selective inhibitor of nuclear export (SINE)/exportin 1 (XPO) inhibitor selinexor for progressive/relapsed ATRT and extra-cranial MRT (NCT05952687) except idasanutlin was withdrawn by the pharmacy sponsor, owing to insufficient tolerability and efficacy in a larger global study (Center, 2024). Other small-molecule MDM2 inhibitors have entered into adult early phase clinical trials but have thus far demonstrated limited effectiveness and significant thrombocytopenia as a dose-limiting toxicity (DLT) (Wang et al., 2024).

4.2.4 XPO1 blockade

XPO1 is the main nuclear exporter of many key tumor suppressors and growth regulatory proteins which include TP53, CDKN1A/B, and RB1 (Xu et al., 2012). XPO1 is overexpressed in many cancer types and has been associated with poor survival outcomes (Turner et al., 2012; Galinski et al., 2021). In silico analysis of MRT patient samples by Coutinho et al. revealed aberrant activation of XPO1. XPO1 inhibition resulted in in vitro cell cycle arrest and apoptosis in MRT cell lines as well as significant tumor growth inhibition in MRT PDX models (Coutinho et al., 2022).

Selinexor (KPT-330) is an orally bioavailable CNS-penetrant XPO1 inhibitor that has demonstrated promising results in adult clinical trials and preclinical efficacy in multiple pediatric cancer models including CNS tumors (Galinski et al., 2021; Attiyeh et al., 2016). Selinexor has been evaluated by the COG in a phase 1 trial for recurrent/refractory solid and CNS tumors (ADVL1414, NCT02323880). Although no objective responses were seen, 13.5 % of patients experienced prolonged (>16 weeks) SD. Toxicity was tolerable on once weekly dosing and the RP2D was

determined to be 35 mg/m^2/dose weekly (Green et al., 2025). A multicenter phase 2 study of selinexor for Wilms tumor and other solid tumors (NCT05985161) that is being spearheaded by the Memorial Sloan Kettering Cancer Center is underway.

4.3 Other associated signaling pathways

4.3.1 PI3K pathway inhibition

The phosphatidylinositol-3 kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) signaling transduction pathway is frequently activated in pediatric cancers and plays a major role in cancer cell proliferation and survival (Toson et al., 2022). While initial responses to PI3K pathway inhibition are encouraging, durability tends to be limited owing to mostly cytostatic responses, suggesting that patients may benefit the most from combination strategies (Hua et al., 2019). Rubens et al. were the first to identify the PI3K pathway as an important driver of ATRT tumorigenicity (Rubens et al., 2017). Furthermore, their group identified activation of mTOR complex (mTORC) 1 and mTORC2, with mTORC2 more broadly and strongly upregulated than mTORC1, in ATRT.

Sirolimus (also known as rapamycin) and everolimus (RAD001) are two mTOR inhibitors that have been tested extensively in several cancers including pediatric CNS tumors (Toson et al., 2022). While both sirolimus and everolimus are mTORC1 inhibitors, everolimus is more effective in inhibiting mTORC2 while sirolimus lacks such ability (Jin et al., 2014). In a phase 1 study of everolimus in pediatric recurrent/refractory solid tumors (NCT00187174), everolimus was well tolerated and the RP2D was 5 mg/m2. Although no objective responses were reported, 6 of 26 patients experienced prolonged (4 or more courses) disease control but did not include the 1 enrolled patient with ATRT (Fouladi et al., 2007). Everolimus combined with ribociclib was evaluated by the Pediatric Brain Tumor Consortium (PBTC) in a phase 1 setting for recurrent/refractory malignant brain tumors (PBTC-050, NCT03387020). The RP2D of everolimus and ribociclib was determined to be 1.2 mg/m^2/day and 120 mg/m^2/day, respectively. Although the combination was well-tolerated, there were no observed objective responses and 16 of 18 evaluable patients developed disease progression while on therapy (DeWire et al., 2021). This same combination was evaluated in Arm B of the (AcSé-ESMART) phase I/II trial (NCT02813135) in a heterogenous group of refractory/relapsed pediatric malignancies. Although no objective responses were seen, disease stability was observed in 41.2 % of patients. RP2D from this trial was

determined to be higher at 2.5 mg/m^2/day and 175 mg/m^2/day for everolimus and ribociclib, respectively (Bautista et al., 2021).

Sapanisertib (TAK-228, MLN0128, INK128) is a highly selective ATP-competitive inhibitor of mTORC1/2. Sapanisertib as a single agent slowed ATRT cell growth and extended survival by nearly 2-fold in mouse xenograft models of ATRT. Remarkably, when combined with cisplatin, sapanisertib led to long-term survival of 40 % of treated mice (Rubens et al., 2017). Pathway analysis after treatment with sapanisertib revealed disruption of the nuclear factor erythroid 2-related factor 2 (Nrf2)-mediated oxidative stress response (Parkhurst et al., 2022). Based on these findings, combination treatment with the CNS penetrant borane (BH3) mimetic obatoclax (GX15–070) was performed. BH3 mimetics function as antagonists of apoptosis regulator protein B-cell lymphoma 2 (Bcl-2), thereby promoting tumor apoptosis (Townsend et al., 2021). The combination of sapanisertib and obatoclax further slowed tumor growth and significantly extended survival time in ATRT orthotopic xenograft models (Parkhurst et al., 2022).

The aforementioned findings led to interest in the use of the highly CNS penetrant dual PI3K/mTOR inhibitor paxalisib for ATRT. While paxalisib monotherapy can slow tumor growth and extend survival in mouse models of ATRT, limited durability of single agent therapy prompted the Johns Hopkins University group to explore rational combination regimens. Findlay et al. demonstrated that paxalisib and gemcitabine combine synergistically to suppress growth and kill ATRT cells across molecular subtypes. Additionally, the combination led to significant survival extension in ATRT-TYR (BT37) and ATRT-MYC (CHLA06) orthotopic xenograft models (Findlay et al., 2024). Metselaar et al. discovered that gemcitabine induces degradation of sirtuin 1 (SIRT), resulting in cell death via activation of p53 and NF-κβ. Gemcitabine treatment resulted in > 30 % increase in median survival time and yielded long term survivors in patient-derived ATRT xenograft mouse models (Metselaar et al., 2024). An upcoming trial from the Pediatric Neuro-Oncology Consortium (PNOC) will look at the combination of paxalisib and gemcitabine as part of an adaptive umbrella trial design framework (PNOC035) for recurrent/refractory ATRT. Paxalisib in combination with the novel highly CNS penetrant HDAC1/3 inhibitor RG2833 or the highly CNS penetrant MEK inhibitor mirdametinib have also shown promise in in vivo models of ATRT (Findlay et al., 2022; Malebranche et al., 2023).

The NCI-COG phase 2 pediatric MATCH trial APEC1621D (NCT03213678) looked at samotolisib (LY3023414), an orally bioavailable

dual PI3K/mTOR inhibitor for relapsed/refractory solid and CNS tumors but found no signs of efficacy (Laetsch et al., 2024). Notably, more than 75 % of tumors from study patients had other actionable genomic alterations identified, suggesting that single agent PI3K/mTOR pathway inhibition is likely clinically insufficient in genomically complex malignancies. Notably, this trial did not include any patients with ATRT, an entity known to be epigenetically heterogenous yet remarkably genomically simple (Lee et al., 2012).

4.3.2 MAPK pathway inhibition

ATRT possess elevated levels of maternal embryonic leucine zipper kinase (MELK) compared to normal brain tissue (Meel et al., 2020). The serine/threonine kinase MELK is an important downstream mediator of the MAPK signaling pathway and has been implicated in the maintenance of cancer stem cell-like states (Ganguly et al., 2015; Badouel et al., 2006). The MEK inhibitor binimetinib (MEK162) suppressed the growth of ATRT flank xenografts but was not effective against orthotopic (intracranial) xenografts, raising concern that binimetinib may not achieve sufficient drug levels in the CNS (Shahab et al., 2020). Meel et al. demonstrated that the combination of the MEK inhibitor trametinib (GSK1120212) with the MELK inhibitor OTSSP167 (OTS167) significantly lengthened survival in their ATRT-SHH orthotopic mouse xenograft model that was not observed with either drug alone. Consistent with the aforementioned findings, Pauck et al. conducted in vitro high throughput drug screening in ATRT cell lines and found specific sensitivity to MEK inhibitors (Pauck et al., 2025). Trametinib in combination with ribociclib has been evaluated by the St. Jude group in stratum B of their phase 1 molecular driven doublet therapies study for refractory/recurrent CNS tumors including ATRT SJDAWN, NCT03434262. For stratum B which was mostly composed of high-grade gliomas (53 %), 6-, 12- and 24-month PFS was dismal at 18 %, 4 % and 0 % (Robinson et al., 2024).

4.3.3 LIN28/Let-7 pathway inhibition

Lin28 homolog A (LIN28A) and LIN28B are key oncogenic drivers of cancer stemness via negative regulation of the maturation of Let-7 microRNA (miRNA) family members (Li et al., 2012; Zhou et al., 2013). LIN28A/B is highly expressed in ATRT primary tumors and cell lines, and LIN28A knockdown suppresses ATRT tumor growth (Weingart et al., 2015). Choi et al. showed that LIN28B overexpression is likely mediated

by SMARCB1 loss in ATRT (Choi et al., 2016). One of the canonical downstream targets of LIN28 is the mTOR pathway, and mTOR pathway inhibitors have demonstrated efficacy against ATRT (Rubens et al., 2017; Findlay et al., 2022; Zhu et al., 2011).

The anti-protozoan drug difluoromethylornithine (DFMO) is a selective inhibitor of ornithine decarboxylase (ODC), the rate limiting step in the polyamine biosynthesis pathway, and has recently been repurposed as an anti-cancer agent. ODC modulates eIF-5A via inhibition of polyamine synthesis and has been shown to directly influence the LIN28/Let-7 axis (Schramm et al., 2025). Kannapan et al. demonstrated that DFMO induced apoptosis in ATRT cells and synergized when combined with the deoxyhypusine synthase (DHPS) inhibitor GC7 (N^1-guanyl-1,7-diaminoheptane) (Kannappan et al., 2019). Dual targeting of polyamine synthesis therefore is an attractive potential therapeutic strategy for ATRT.

4.3.4 Other signal transduction pathway inhibitors

Cancer cells heavily rely on the activation of multiple receptor tyrosine kinases (RTKs) to sustain robust oncogenic signaling (Lemmon & Schlessinger, 2010). RTKs therefore serve as attractive targets for cancer therapy and a multitude of tyrosine kinase inhibitors (TKIs) have already been clinically approved for a wide variety of cancer types. Preclinical studies indicate that ATRT cells overexpress polo-like kinases (PLK) 1 and 4 (Sredni et al., 2017; Alimova et al., 2017). Treatment with the PLK1 inhibitor volasertib (BI 6727) significantly inhibited cell growth, inhibited clonogenic potential, suppressed tumor-sphere formation, and significantly induced radiosensitivity of ATRT cells (Alimova et al., 2017). PLK4 inhibition using CFI-400945 also demonstrated in vitro cytotoxicity against ATRT cell lines (Sredni et al., 2017). Drug compound screening performed by Singh et al. determined that agents capable of modulating pathways constituting epidermal growth factor receptor-receptor tyrosine (EGFR)-erythroblastic oncogene B (ErbB2, more commonly referred to as human epidermal growth factor 2/HER2), mTOR, PLK, or AURKA were effective against ATRT cell lines. EGFR-ErbB2 pathway inhibition using the small molecule inhibitor dual TKI lapatinib has exhibited both in vitro and in vivo efficacy against ATRT (Singh et al., 2013).

High throughput drug screening of ATRT tumoroid models by Paasen et al. revealed ATRT-MYC subgroup-specific vulnerability to multi-TKIs (mTKIs), most notably to pazopanib and lenvatinib (Paassen et al., 2023). ATRT-MYC tumoroids had high basal levels of phosphorylated fibroblast

growth factor receptor 2 (FGFR2) and platelet-derived growth factor receptor alpha (PDGFRα) that was abrogated by mTKI treatment. Interestingly, Wong et al. previously showed that dual targeting of PDGFRα and FGFR1 displayed in vitro synergistic efficacy against MRT cells (Wong et al., 2016). In an earlier study by Torchia et al., integrated genomic analysis revealed differential methylation of a platelet derived growth factor receptor B (PDGFRB)-associated enhancer in group 2 A (corresponding to ATRT-MYC) ATRT tumors. ATRT-MYC tumors demonstrated PDGFRB overexpression and in vitro sensitivity to the mTKIs nilotinib and dasatinib (Torchia et al., 2016). Consistent with these findings, initial testing by the PPTP also showed the ATRT-MYC cell line CHLA-266 among the most sensitive to dasatinib (Kolb et al., 2008).

Paasen et al. also described a subset of ATRT-SHH tumors showing high sensitivity to Notch inhibitors that corresponded with high expression of Notch receptors (Paassen et al., 2023). Notch signaling pathway inhibition can be achieved using gamma (γ)-secretase inhibitors (GSI) which prevent the final cleavage step of its precursor form that releases the Notch intracellular domain (NICD) (Olsauskas-Kuprys et al., 2013). A phase 1 trial of the GSI MK-0752 for pediatric refractory CNS tumors by the PBTC (PBTC-024, NCT00572182) failed to show any objective responses and most patients experienced disease progression after 1 to 2 cycles (Fouladi et al., 2011). Nirogacestat is a novel orally bioavailable GSI that has shown antitumor activity in patients with desmoid tumor (Gounder et al., 2023). Nirogacestat, however, has poor CNS penetration due to its high serum protein binding properties (Bui, 2023).

4.4 Integrated stress response (ISR)

4.4.1 Proteasome inhibition

SMARCB1-deficient malignancies exhibit dramatic activation of the unfolded protein response (UPR) and endoplasmic reticulum (ER) stress response via the MYC-$p19^{ARF}$-MDM2-p53 axis, and consequently display exquisite sensitivity to proteasome inhibitors (Carugo et al., 2019). Bortezomib (PS-341) inhibited in vitro cellular proliferation and induced apoptosis via p53 accumulation in ATRT-MYC PDX cell lines. Additionally, bortezomib repressed tumor growth and prolonged survival in ATRT-MYC orthotopic xenograft mice (Tran et al., 2020).

Unbiased drug screening of ATRT cell lines by Morin et al. identified proteasome inhibitors as being highly effective in vitro. The CNS-penetrant proteasome inhibitor marizomib (salinosporamide A, NPI-0052)

demonstrated in vitro efficacy against ATRT cell lines. Moreover, marizomib inhibited tumor growth and significantly extended survival in ATRT PDX xenograft mice (Morin et al., 2020). The orally bioavailable CNS-penetrant proteasome inhibitor ixazomib (MLN2238) also demonstrated in vitro activity against ATRT (Carugo et al., 2019). Novak et al. demonstrated in vitro synergistic activity of ixazomib with gemcitabine or idarubicin against established ATRT cell lines (Novak et al., 2023). Notably, ixazomib in combination with gemcitabine and doxorubicin is being studied in the phase 2 setting for SMARCB1-negative renal malignancies (NCT03587662) (Msaouel et al., 2019).

4.4.2 Anti-apoptotic inhibition

Pharmacogenomic analysis showed that ATRT-SHH cell clines are enriched for multiple B-cell lymphoma 2 (bcl-2) and heat shock protein 90 (HSP90) inhibitors (Paassen et al., 2023). The anti-apoptotic Bcl-2 family of proteins helps regulate cell proliferation and plays a critical role in tumor formation and chemotherapy resistance (Qian et al., 2022). Heat shock proteins are found in increased levels in many cancers and act as molecular chaperones for many oncogenic proteins to provide potentially lethal stress from the hostile hypoxic and acidotic tumor microenvironment (TME) (Mahalingam et al., 2009). Coyle et al. also demonstrated expression of several members of the inhibitor of apoptosis (IAP) family of proteins in MRT cells and tissue (Coyle et al., 2022). Several anti-apoptotic inhibitors have shown preclinical efficacy in ATRT and MRT cell lines including obatoclax (Parkhurst et al., 2022), the X-linked inhibitor of apoptosis protein (XIAP) inhibitor embelin (Coyle et al., 2022), and the protein-translation inhibitor homoharringtonine (Howard et al., 2020).

4.4.3 Metabolic targeting

In the malignant state, rapid cellular proliferation drives dependency on distinct metabolic pathways to support high energy demands for increased utilization of nucleic acids and amino acids and to protect against reactive oxygen species (ROS) (Alva et al., 2023). Unbiased metabolic profiling demonstrated that high MYC-expressing ATRT patient cell lines were dependent on glutamine signaling and sensitive to glutamine metabolic inhibition by 6-diazo-5-oxo-L-norleucine (DON) (Wang et al., 2019). DON as a single agent significantly improved survival in orthotopic ATRT-MYC mouse models and combined synergistically with carboplatin to further improve survival. Nakata et al. also showed that DON decreased histone trimethylation in ATRT cell lines and

demonstrated in vitro synergistic activity when combined with tazemetostat (Nakata et al., 2020). While further development of DON for clinical use was impeded by its dose-limiting gastrointestinal toxicities, DON prodrugs are currently under development for adult solid tumors (Novotná et al., 2024). Among these is the CNS penetrant JHU-395 which has demonstrated preclinical in vitro and in vivo efficacy albeit in another MYC-driven CNS tumor type (Pham et al., 2021).

5. Promise of immunotherapeutic strategies for ATRT

ATRT has one of the lowest tumor mutational burden of all pediatric malignancies, lending itself to the lack of suitable tumor-specific antigens (neoantigens) for presentation to the adaptive and innate immune system to generate an anti-tumor immune response (Torchia et al., 2016). Although ATRT is known to be generally immunoquiescent, immune profiling has revealed that these tumors are more immunologically active compared to other pediatric CNS tumors (Tran et al., 2023a). ATRT is significantly infiltrated by a greater number of clusters of differentiation (CD)8+ TILs compared to high-grade glioma (HGG) and medulloblastoma. Similar to HGG and medulloblastoma, ATRT has moderate infiltration of CD68+ tumor-associated macrophages (TAMs) and CD4+ TILs (Lu et al., 2012). The TME in ATRT, however, has been demonstrated to vary by molecular subtype, with ATRT-MYC tumors (also extracranial MRTs) having the highest level of TILs in its TME compared to ATRT-TYR and ATRT-SHH (Chun et al., 2019; Safaei et al., 2021). Genomic analysis of immunologic correlates in ATRT by Panwalker et al. revealed that polybromo-1 (PBRM1) expression levels were associated with immune composition. Low expression of PBRM1, a core subunit of the polybromo-associated factor (PBAF) SWI/SNF complex, was inversely correlated with degree of CD8+ T-cell infiltration and associated with better overall prognosis. Conversely, CD163+ TAMs were significantly associated with high PBRM1 expression (Panwalkar et al., 2020).

5.1 Immune checkpoint inhibition

Immune profiling has shown that the immune checkpoint molecule programmed death-ligand (PD-L1) is more highly expressed in ATRT compared to other pediatric CNS tumors. Leruste et al. described the heterogeneity of immune infiltrates in ATRT that include exhausted T effector cells and an abundance of immunosuppressive myeloid derived

suppressor cells (MDSCs) (Leruste et al., 2019). The above findings thus provide rationale for the use of immune checkpoint inhibitors for ATRT. Several studies using PD-1/PD-L1 inhibitors combined with either cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) or T cell immunoreceptor with Ig and immunoreceptor tyrosine-based inhibitory motif (ITIM) domains (TIGIT) blockade for SMARCB1/SMARCA4-deficient tumors are underway (NCT05286801, NCT04416568).

5.2 Combined epigenetic dysregulation and immune checkpoint inhibition

The histone methyltransferase EZH2 has been shown to facilitate epigenetic silencing of MHC Class I antigen presentation genes in cancer (Burr et al., 2019). Additionally, EZH2 inhibition can enhance tumor immunogenicity through derepression of endogenous retroviruses and induction of IFN-γ response (Ishak et al., 2016; Jayabal et al., 2021). Several studies have explored the combination of EZH2 inhibition with immune checkpoint inhibition (ICI) and demonstrated significant immunological killing in several cancer types by promoting CD8+ T cell infiltration and reprogramming of regulatory T cells in the immune TME (Emran et al., 2019; Wang et al., 2018). TAZNI is an ongoing phase 1/2 combination trial of tazemetostat with nivolumab (PD-1) and ipilimumab (CTLA-4) for pediatric INI1-negative or SMARCA4-deficient tumors including ATRT (NCT05407441).

5.3 Vaccine-based therapy

Cancer or tumor vaccines deliver a concentrated source of tumor-associated and/or tumor-specific antigens in order to generate an anti-tumor immune response. Challenges to this approach for use in ATRT include a paucity of tumor-derived neoantigens from somatic mutations in this genomically quiescent entity as well as suppression of MHC I class molecules for antigen presentation (Torchia et al., 2016; Tran et al., 2023a). Nevertheless, several DC vaccine-based studies using autologous dendritic cells (DCs) have been conducted in ATRT patients. Ardon et al. treated 45 pediatric patients with relapsed CNS tumors with autologous DCs loaded with tumor lysate, which included 3 ATRT patients who experienced prolonged disease remission (Ardon et al., 2010). In a later DC vaccine study by Van Gool et al., 3 of 7 ATRT patients achieved long-term survival with observable CD8+ T cell responses in 2 analyzed patients (van Gool et al., 2016). No significant adverse events were noted in both studies (Ardon et al., 2010; van Gool et al., 2016).

5.4 Oncolytic viral therapy

Oncolytic viruses possess the ability to selectively propagate and destroy cancer tissue while causing minimal damage to surrounding normal tissue (Parato et al., 2005). MV-NIS is an Edmonston lineage oncolytic measles virus that expresses the human sodium iodide symporter (hNIS) (Myers et al., 2007). MV-NIS preferentially binds to complement inactivating factor CD46 (also known as membrane cofactor protein/MCP), which plays a pivotal role in tumor growth and metastases (Geller & Yan, 2019). Preclinical studies using MV-NIS have exhibited viral targeting and replicability of ATRT in cells in vitro and additionally, prolonged survival in intracranial and metastatic mouse xenograft models of ATRT (Studebaker et al., 2015). MV-NIS has been evaluated in a phase 1 trial by PNOC for recurrent medulloblastoma and ATRT (PNOC005, NCT02962167). This trial which included 4 (of 34) patients with ATRT was safe and well-tolerated and preliminary analysis indicated anti-viral effects in tumors (Kline et al., 2024). Other oncolytic viral therapies have also demonstrated preclinical efficacy against ATRT including herpes simplex virus-1 (HSV1) rRp450 and adenovirus Delta-24-RGD (DNX-2401, tasadenoturev) (Studebaker et al., 2017; Garcia-Moure et al., 2021). A phase 1 trial of another modified HSV-1 vector G207 for recurrent/refractory cerebellar tumors including ATRT is currently open (NCT03911388).

5.5 Radioimmunotherapy

Radioimmunotherapy (RIT), which involves intra-compartmental delivery of radionuclides that selectively target cancer-associated cell surface antigens using monoclonal antibodies, is a promising approach for CNS tumors. Intra-compartmental RIT permits the delivery of a high dose of therapeutic RT to CNS tumor cells while minimizing exposure to surrounding normal brain tissue (Larson et al., 2015). The use of radiation also upregulates expression of major histocompatibility complex (MHC) on tumor cell surfaces and releases damage-associated molecular pattern (DAMP) molecules such as ATP from tumor cells to induce immunogenic cell death (Donlon et al., 2021). Candidate antigens are ideally those that are highly expressed on the cell surface of CNS tumors but have little to no expression in normal brain tissue. B7 Homolog 3 (B7-H3, encoded by CD276) is an immune checkpoint molecule that is broadly expressed in pediatric CNS malignancies including ATRT (Maachani et al., 2020; Theruvath et al., 2020). Although initially highly expressed in fetal brain

Table 3 Targeted agents under consideration for the treatment of ATRT.

Agent	Target	Mouse in vivo data?	Adult RP2D?	Pediatric RP2D?
Epigenetic modifiers				
Vorinostat	pan-HDAC	Yes	Yes	Yes
Panobinostat	HDAC	Yes	Yes	Yes
RG2833	HDAC 1,3	Yes	No	No
Entinostat	HDAC 1,3	No	Yes	Yes
Quisinostat	HDAC 1,2	Yes	Yes	No
Tazemetostat	EZH2	Yes	Yes	Yes
JQ1	BRD4/MYC	Yes	Yes	Yes
Decitabine	DNMT	No	Yes	Yes
Ezobresib (BMS-986158)	pan-BET	No	Yes	No
Trotabresib (BMS-986378)	pan-BET	No	Yes	No
Curaxin (CBL0137)	FACT	Yes	Yes	Yes
Cell cycle targeting				
Alisertib	AURKA	Yes	Yes	Yes
Palbociclib	CDK4/6	Yes	Yes	Yes
Ribociclib	CDK4/6	Yes	Yes	Yes
Abemaciclib	CDK4/6	Yes	Yes	Yes
Idasanutlin	MDM2/p53	Yes	Yes	Yes
Selinexor	XPO1	Yes	Yes	Yes
Signal transduction pathway inhibitors				
Everolimus	mTOR	No	Yes	Yes
Sapanisertib	mTOR	Yes	Yes	No
Samotolisib	PI3K/mTOR	No	Yes	Yes
Paxalisib	PI3K/mTOR	Yes	Yes	Yes

OTSSP167/OTS167	MELK	Yes	Yes	No
Binimetinib	MEK	Yes	Yes	Yes
Trametinib	MEK	Yes	Yes	Yes
Selumetinib	MEK	No	Yes	Yes
Mirdametinib	MEK	Yes	Yes	Yes
DFMO	ODC/ Lin28B/Let-7	Yes	Yes	Yes
AMXT-1501	Lin28B/Let-7	No	Yes	No
Volasertib	PLK1	Yes	Yes	Yes
Lapatinib	RTK/EGFR	Yes	Yes	Yes
Dasatinib	PDGFRB	Yes	Yes	Yes
Cellular stress activators				
Bortezomib	Proteasome	Yes	Yes	Yes
Marizomib	Proteasome	Yes	Yes	Yes
Ixazomib	Proteasome	Yes	Yes	Yes
Obatoclax	Bcl-2	Yes	Yes	No
DON	Glutamine	Yes	Yes	Yes
JHU-395	Glutamine	Yes	No	No

tissue, B7-H3 expression becomes negligent postnatally due to post-transcriptional regulation (Theruvath et al., 2020). The radiolabeled monoclonal antibody (iodine-131–8H9) omburtamab has been evaluated in a phase 1 study for intraventricular delivery in B7-H3-expressing CNS malignancies including ATRT (Kramer et al., 2022). Although ^{131}I-omburamab was safe and showed favorable dosimetry, further clinical development for CNS tumors has been halted by the drug company.

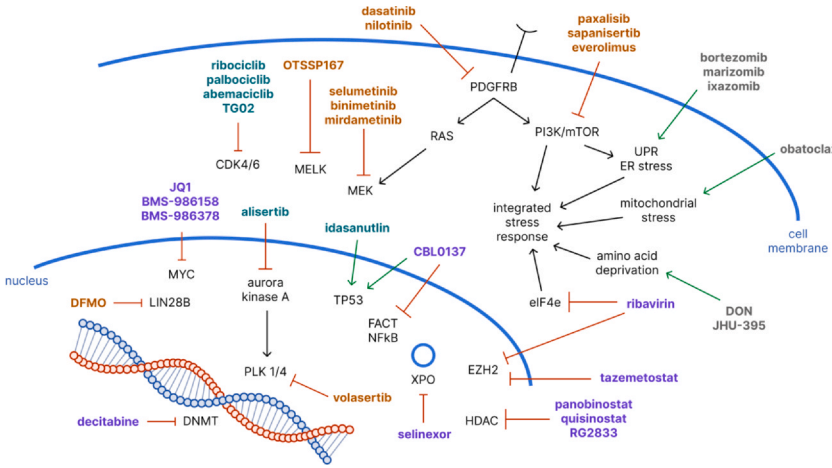

Fig. 2 Cartoon schema of targeted agents under consideration for use in ATRT. Targeted agents are color coded as follows: epigenetic modifiers (purple), cell cycle inhibitors (dark cyan), signal transduction pathway inhibitors (dark orange), cellular stress activators (dark gray). Some agents act on multiple pathway/targets which are not depicted in the above figure.

5.6 Chimeric antigen receptor (CAR) therapy

CARs are an emerging class of immunotherapy comprised of recombinant receptors that provide both antigen-binding and T-cell (CAR-T) (or NK cell/CAR-NK) activating functions (Sadelain et al., 2013). While CAR-T therapy has met with success in hematologic malignancies, its use against solid tumors including CNS tumors has demonstrated limited response rates, largely owing to the immunosuppressive TME, which impairs CAR-T proliferation and persistence and results in CAR-T exhaustion (Irving et al., 2017). Newer generations of CAR products including CAR-NK are being engineered to overcome immunosuppressive barriers and enhance antitumor responses against solid tumors.

B7-H3 is broadly expressed in pediatric CNS tumors including ATRT (Maachani et al., 2020; Theruvath et al., 2020). Theruvath et al. demonstrated that B7-H3 is expressed at similar levels across the 3 ATRT molecular subgroups (Theruvath et al., 2020). B7-H3 CAR-T cells were highly active against ATRT cells and xenograft mouse models. Additionally, B7-H3 CAR-T cells administered either via intraventricular or intravenous route mediated immunological memory and protected from tumor rechallenge. Several early phase clinical trials using B7-H3 CAR-T cell therapy for

pediatric relapsed/recurrent CNS tumors including ATRT are underway (NCT05835687, NCT04185038, NCT04897321, NCT05768880).

Glypican 3 (GPC3) is a heparan sulfate proteoglycan and oncofetal protein that is highly expressed on the cell surface of several pediatric solid embryonal tumors including ATRT (Chan et al., 2013; Kohashi et al., 2013). GPC3 activates the canonical Wnt/ß-catenin pathway (Ortiz et al., 2019). Unlike B7-H3 which has negligible expression in normal tissue postnatally, GPC3 can be physiologically expressed in normal tissues during the first year of life (Kinoshita et al., 2015). To mitigate this age-associated risk, phase 1 clinical trials utilizing GPC3 CAR-T therapy have an inclusion criteria of > 1 year of age. Several early phase GPC3 CAR-T trials are currently open to enrollment for pediatric solid tumors expressing GPC3 including ATRT (NCT04715191, NCT04377932, NCT05103631). Other CAR-T cell therapy antigen targets under clinical investigation for ATRT include EGFR, GD2, and HER2 (Tran et al., 2023a). Toxicities related to immune-mediated tumor inflammation including pseudoprogression and tumor inflammation-associated neurotoxicity (TIAN) have been documented in patients receiving CAR-T therapies, ICIs or vaccine-based therapy (Tran et al., 2023a).

Table 3 lists targeted agents that are under investigation for the treatment of ATRT (See Fig. 2).

6. Summary

Outcomes for ATRT have improved with aggressive multimodality approaches that incorporate maximal safe resection, intensive chemotherapy, and RT. Nevertheless, ATRT patients remain at high risk for relapse and long-term treatment-related adverse effects, hence the need to develop novel targeted therapies for this hard-to-treat disease. ATRT is fundamentally an epigenetic disease and thus likely to respond to targeting its epigenetic vulnerabilities, ideally utilizing combination strategies alongside chemoradiation and/or other targeted agents. Compared to other pediatric CNS tumors, ATRT is relatively immunogenic, thus supporting investigation into new avenues for cancer immunotherapy.

References

Al Shoyaib, A., et al. (2021). The effect of histone deacetylase inhibitors panobinostat or entinostat on motor recovery in mice after ischemic stroke. *Neuromolecular Medicine, 23*(4), 471–484.

Alimova, I., et al. (2013). Inhibition of EZH2 suppresses self-renewal and induces radiation sensitivity in atypical rhabdoid teratoid tumor cells. *Neuro-Oncology, 15*(2), 149–160.
Alimova, I., et al. (2019). Inhibition of MYC attenuates tumor cell self-renewal and promotes senescence in SMARCB1-deficient group 2 atypical teratoid rhabdoid tumors to suppress tumor growth in vivo. *International Journal of Cancer, 144*(8), 1983–1995.
Alimova, I., et al. (2017). Targeting Polo-like kinase 1 in SMARCB1 deleted atypical teratoid rhabdoid tumor. *Oncotarget, 8*(57), 97290–97303.
Alimova, I., et al. (2022). Targeting the TP53/MDM2 axis enhances radiation sensitivity in atypical teratoid rhabdoid tumors. *International Journal of Oncology, 60*(3).
Alva, E., et al. (2023). Recent progress and novel approaches to treating atypical teratoid rhabdoid tumor. *Neoplasia (New York, N. Y.), 37*, 100880.
Alver, B. H., et al. (2017). The SWI/SNF chromatin remodelling complex is required for maintenance of lineage specific enhancers. *Nature Communications, 8*(1), 14648.
Ardon, H., et al. (2010). Adjuvant dendritic cell-based tumour vaccination for children with malignant brain tumours. *Pediatric Blood & Cancer, 54*(4), 519–525.
Aridgides, P. D., et al. (2023). Focal versus craniospinal radiation for disseminated atypical teratoid/rhabdoid tumor following favorable response to systemic therapy. *Pediatric Blood & Cancer, 70*(7), e30351.
Athale, U. H., et al. (2009). Childhood atypical teratoid rhabdoid tumor of the central nervous system: A meta-analysis of observational studies. *Journal of Pediatric Hematology/Oncology: Official Journal of the American Society of Pediatric Hematology/Oncology, 31*(9), 651–663.
Attiyeh, E. F., et al. (2016). Pharmacodynamic and genomic markers associated with response to the XPO1/CRM1 inhibitor selinexor (KPT-330): A report from the pediatric preclinical testing program. *Pediatric Blood & Cancer, 63*(2), 276–286.
Badouel, C., et al. (2006). M-phase MELK activity is regulated by MPF and MAPK. *Cell Cycle (Georgetown, Tex.), 5*(8), 883–889.
Bartelheim, K., et al. (2016). Improved 6-year overall survival in AT/RT – results of the registry study rhabdoid 2007. *Cancer Medicine, 5*(8), 1765–1775.
Bautista, F., et al. (2021). Phase I or II study of ribociclib in combination with topotecan-temozolomide or everolimus in children with advanced malignancies: Arms a and b of the AcSé-ESMART trial. *Journal of Clinical Oncology, 39*(32), 3546–3560.
Beckwith, J. B., & Palmer, N. F. (1978). Histopathology and prognosis of wilms tumors: Results from the first national wilms' tumor study. *Cancer, 41*(5), 1937–1948.
Benesch, M., et al. (2014). High-dose chemotherapy (HDCT) with auto-SCT in children with atypical teratoid/rhabdoid tumors (AT/RT): A report from the european rhabdoid registry (EU-RHAB). *Bone Marrow Transplantation, 49*(3), 370–375.
Biegel, J. A., Busse, T. M., & Weissman, B. E. (2014). SWI/SNF chromatin remodeling complexes and cancer. *American Journal of Medical, 166c*(3), 350–366.
Biggs, P. J., et al. (1987). Malignant rhabdoid tumor of the central nervous system. *Human Pathology, 18*(4), 332–337.
Bonnin, J. M., et al. (1984). The association of embryonal tumors originating in the kidney and in the brain. A report of seven cases. *Cancer, 54*(10), 2137–2146.
Braal, C. L., et al. (2021). Inhibiting CDK4/6 in breast cancer with palbociclib, ribociclib, and abemaciclib: Similarities and differences. *Drugs, 81*(3), 317–331.
Bruggers, C. S., et al. (2011). Clinicopathologic comparison of familial versus sporadic atypical teratoid/rhabdoid tumors (AT/RT) of the central nervous system. *Pediatric Blood & Cancer, 56*(7), 1026–1031.
Bui, N. (2023). *Phase 2 Study of Cryoablation and Nirogacestat for Desmoid Tumor (NCT-05949099),* 16.

Bukowinski, A., et al. (2021). A phase 1 study of entinostat in children and adolescents with recurrent or refractory solid tumors, including CNS tumors: Trial ADVL1513, pediatric early Phase-Clinical trial network (PEP-CTN). *Pediatric Blood & Cancer, 68*(4), e28892.
Burr, M. L., et al. (2019). An evolutionarily conserved function of polycomb silences the MHC class I antigen presentation pathway and enables immune evasion in cancer. *Cancer Cell, 36*(4), 385–401.e8.
Buscariollo, D. L., et al. (2012). Survival outcomes in atypical teratoid rhabdoid tumor for patients undergoing radiotherapy in a surveillance, epidemiology, and end results analysis. *Cancer, 118*(17), 4212–4219.
Carol, H., et al. (2011). Efficacy and pharmacokinetic/pharmacodynamic evaluation of the aurora kinase a inhibitor MLN8237 against preclinical models of pediatric cancer. *Cancer Chemotherapy and Pharmacology, 68*(5), 1291–1304.
Carol, H., et al. (2014). Initial testing (stage 1) of the histone deacetylase inhibitor, quisinostat (JNJ-26481585), by the pediatric preclinical testing program. *Pediatric Blood & Cancer, 61*(2), 245–252.
Carugo, A., et al. (2019). p53 Is a master regulator of proteostasis in SMARCB1-Deficient malignant rhabdoid tumors. *Cancer Cell, 35*(2), 204–220.e9.
Casaos, J., et al. (2018). Ribavirin as a potential therapeutic for atypical teratoid/rhabdoid tumors. *Oncotarget, 9*(8), 8054–8067.
Center, P. M. (2024). Disappointing results with idasanutlin in children with solid tumors. Available from https://research.prinsesmaximacentrum.nl/en/disappointing-results-with-idasanutlin-in-children-with-solid-tumors-1.
Chan, E. S., et al. (2013). Immunohistochemical expression of glypican-3 in pediatric tumors: an analysis of 414 cases. *Pediatric and Developmental Pathology: the Official Journal of the Society for Pediatric Pathology and the Paediatric Pathology Society, 16*(4), 272–277.
Chan, V., et al. (2018). A systematic review of atypical teratoid rhabdoid tumor in adults. *Frontiers in Oncology, 8*, 567.
Chi, S. N., et al. (2009). Intensive multimodality treatment for children with newly diagnosed CNS atypical teratoid rhabdoid tumor. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology, 27*(3), 385–389.
Chi, S. N., et al. (2022). Update on phase 1 study of tazemetostat, an enhancer of zeste homolog 2 inhibitor, in pediatric patients with relapsed or refractory integrase interactor 1–negative tumors. *Journal of Clinical Oncology, 40*(16_suppl) 10040-10040.
Choi, S. A., et al. (2016). LIN28B is highly expressed in atypical teratoid/rhabdoid tumor (AT/RT) and suppressed through the restoration of SMARCB1. *Cancer Cell International, 16*, 32.
Chong, W. C., et al. (2021). Atypical teratoid rhabdoid tumours are susceptible to panobinostat-mediated differentiation therapy. *Cancers (Basel), 13*(20).
Chun, H. E., et al. (2019). Identification and analyses of Extra-Cranial and cranial rhabdoid tumor molecular subgroups reveal tumors with cytotoxic t cell infiltration. *Cell Reports, 29*(8), 2338–2354.e7.
Cohen, B. H., et al. (2015). Pilot study of intensive chemotherapy with peripheral hematopoietic cell support for children less than 3 years of age with malignant brain tumors, the CCG-99703 phase I/II study. A report from the children's oncology group. *Pediatric Neurology, 53*(1), 31–46.
Coutinho, D. F., et al. (2022). Validation of a non-oncogene encoded vulnerability to exportin 1 inhibition in pediatric renal tumors. *Med, 3*(11), 774–791.e7.
Coyle, R., Sullivan, M. J. O., & Zisterer, D. M. (2022). Targeting inhibitor of apoptosis proteins (IAPs) with IAP inhibitors sensitises malignant rhabdoid tumour cells to cisplatin. *Cancer Treatment and Research Communications, 32*, 100579.
Dang, C. V. (2012). MYC on the path to cancer. *Cell, 149*(1), 22–35.

De la Cruz-Hernandez, E., et al. (2015). Ribavirin as a tri-targeted antitumor repositioned drug. *Oncology Reports, 33*(5), 2384–2392.
Del Baldo, G., et al. (2021). Rhabdoid tumor predisposition syndrome: From clinical suspicion to general management. *Frontiers in Oncology, 11*, 586288.
Delmore, J. E., et al. (2011). BET bromodomain inhibition as a therapeutic strategy to target c-Myc. *Cell, 146*(6), 904–917.
Desai, K., et al. (2024). ATRT-11. Irs-iii: Long-term follow-up shows favorable outcomes and durable responses for localized atypical teratoid rhabdoid tumor (ATRT). *Neuro-Oncology, 26*(Supplement_4) 0-0.
DeWire, M. D., et al. (2021). A phase I and surgical study of ribociclib and everolimus in children with recurrent or refractory malignant brain tumors: a pediatric brain tumor consortium study. *Clinical Cancer Research: an Official Journal of the American Association for Cancer Research, 27*(9), 2442–2451.
Dho, Y. S., et al. (2015). Investigation of the location of atypical teratoid/rhabdoid tumor. *Child's Nervous System: ChNS: Official Journal of the International Society for Pediatric Neurosurgery, 31*(8), 1305–1311.
Ding, A. S., et al. (2021). Targeting of cyclin-dependent kinases in atypical teratoid rhabdoid tumors with multikinase inhibitor TG02. *Journal of Neurosurgery. Pediatrics, 28*(6), 734–743.
Donlon, N. E., et al. (2021). Radiotherapy, immunotherapy, and the tumour microenvironment: Turning an immunosuppressive milieu into a therapeutic opportunity. *Cancer Letters, 502*, 84–96.
Dufour, C., et al. (2012). Clinicopathologic prognostic factors in childhood atypical teratoid and rhabdoid tumor of the central nervous system: A multicenter study. *Cancer, 118*(15), 3812–3821.
Eaton, K. W., et al. (2011). Spectrum of SMARCB1/INI1 mutations in familial and sporadic rhabdoid tumors. *Pediatric Blood & Cancer, 56*(1), 7–15.
Egiz, A., Kannan, S., & Asl, S. F. (2022). The impact of surgical resection and adjuvant therapy on survival in pediatric patients with atypical teratoid/rhabdoid tumor: Systematic review and pooled survival analysis. *World Neurosurgery, 164*, 216–227.
Emran, A. A., et al. (2019). Targeting DNA methylation and EZH2 activity to overcome melanoma resistance to immunotherapy. *Trends in Immunology, 40*(4), 328–344.
Erkek, S., et al. (2019). Comprehensive analysis of chromatin states in atypical teratoid/rhabdoid tumor identifies diverging roles for SWI/SNF and polycomb in gene regulation. *Cancer Cell, 35*(1), 95–110.e8.
Federico, A., et al. (2022). ATRT-SHH comprises three molecular subgroups with characteristic clinical and histopathological features and prognostic significance. *Acta Neuropathologica, 143*(6), 697–711.
Findlay, T., et al. (2024). ATRT-15. Combining the PI3K inhibitor paxalisib with nucleoside analog gemcitabine to improve survival of atypical teratoid/rhabdoid tumors. *Neuro-Oncology, 26*(Supplement_4) 0-0.
Findlay, T., et al. (2022). ATRT-26. The PI3k inhibitor paxalisib combines with the novel HDAC1/3 inhibitor RG2833 to improve survival in mice bearing orthotopic xenografts of atypical teratoid/rhabdoid tumors. *Neuro-Oncology, 24*(Supplement_1) i9-i9.
Finkelstein-Shechter, T., et al. (2010). Atypical teratoid or rhabdoid tumors: Improved outcome with high-dose chemotherapy. *Journal of Pediatric Hematology/Oncology: Official Journal of the American Society of Pediatric Hematology/Oncology, 32*(5), e182–e186.
Fischer-Valuck, B. W., et al. (2017). Assessment of the treatment approach and survival outcomes in a modern cohort of patients with atypical teratoid rhabdoid tumors using The National cancer database. *Cancer, 123*(4), 682–687.
Fossey, M., et al. (2017). Atypical teratoid rhabdoid tumor in the first year of life: The Canadian ATRT registry experience and review of the literature. *Journal of Neuro-Oncology, 132*(1), 155–162.

Fouladi, M., et al. (2007). Phase I study of everolimus in pediatric patients with refractory solid tumors. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology, 25*(30), 4806–4812.
Fouladi, M., et al. (2011). Phase I trial of MK-0752 in children with refractory CNS malignancies: A pediatric brain tumor consortium study. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology, 29*(26), 3529–3534.
Frisch, S., et al. (2024). Radiation therapy plays an important role in the treatment of atypical teratoid/rhabdoid tumors: Analysis of the EU-RHAB cohorts and their precursors. *International Journal of Radiation Oncology, Biology, Physics, 119*(4), 1147–1157.
Frühwald, M. C., et al. (2020). Age and DNA methylation subgroup as potential independent risk factors for treatment stratification in children with atypical teratoid/rhabdoid tumors. *Neuro-Oncology, 22*(7), 1006–1017.
Frühwald, M. C., et al. (2016). Atypical teratoid/rhabdoid tumors-current concepts, advances in biology, and potential future therapies. *Neuro-Oncology, 18*(6), 764–778.
Frühwald, M. C., et al. (2021). Current recommendations for clinical surveillance and genetic testing in rhabdoid tumor predisposition: A report from the SIOPE host genome working group. *Familial Cancer, 20*(4), 305–316.
Galinski, B., et al. (2021). Therapeutic targeting of Exportin-1 in childhood cancer. *Cancers (Basel), 13*(24).
Ganguly, R., et al. (2015). MELK-a conserved kinase: Functions, signaling, cancer, and controversy. *Clinical and Translational Medicine, 4*, 11.
Garcia-Moure, M., et al. (2021). Delta-24-RGD, an oncolytic adenovirus, increases survival and promotes proinflammatory immune landscape remodeling in models of AT/RT and CNS-PNET. *Clinical Cancer Research: an Official Journal of the American Association for Cancer Research, 27*(6), 1807–1820.
Gardner, S. L., et al. (2008). Intensive induction chemotherapy followed by high dose chemotherapy with autologous hematopoietic progenitor cell rescue in young children newly diagnosed with central nervous system atypical teratoid rhabdoid tumors. *Pediatric Blood & Cancer, 51*(2), 235–240.
Gasparian, A. V., et al. (2011). Curaxins: Anticancer compounds that simultaneously suppress NF-κB and activate p53 by targeting FACT. *Science Translational Medicine, 3*(95) 95ra74.
Gastberger, K., et al. (2023). Current molecular and clinical landscape of ATRT - the link to future therapies. *Cancer Management and Research, 15*, 1369–1393.
Geller, A., & Yan, J. (2019). The role of membrane bound complement regulatory proteins in tumor development and cancer immunotherapy. *Frontiers in Immunology, 10*, 1074.
Geoerger, B., et al. (2017). A phase I study of the CDK4/6 inhibitor ribociclib (LEE011) in pediatric patients with malignant rhabdoid tumors, neuroblastoma, and other solid tumors. *Clinical Cancer Research: an Official Journal of the American Association for Cancer Research, 23*(10), 2433–2441.
Geyer, J. R., et al. (2005). Multiagent chemotherapy and deferred radiotherapy in infants with malignant brain tumors: A report from the children's cancer group. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology, 23*(30), 7621–7631.
Ginn, K. F., & Gajjar, A. (2012). Atypical teratoid rhabdoid tumor: Current therapy and future directions. *Frontiers in Oncology, 2*, 114.
Gounder, M., et al. (2023). Nirogacestat, a γ-Secretase inhibitor for desmoid tumors. *The New England Journal of Medicine, 388*(10), 898–912.
Green, A. L., et al. (2025). Phase 1 trial of selinexor in pediatric recurrent/refractory solid and CNS tumors (ADVL1414): A children's oncology group phase 1 consortium trial. *Clinical Cancer Research: an Official Journal of the American Association for Cancer Research*.
Gulati, N., Béguelin, W., & Giulino-Roth, L. (2018). Enhancer of zeste homolog 2 (EZH2) inhibitors. *Leukemia & Lymphoma, 59*(7), 1574–1585.

Gupta, N. K., et al. (2024). Management of atypical teratoid/rhabdoid tumors in the pediatric population: A systematic review and Meta-Analysis. *World Neurosurgery, 181*, e504–e515.
Hashizume, R., et al. (2016). Inhibition of DNA damage repair by the CDK4/6 inhibitor palbociclib delays irradiated intracranial atypical teratoid rhabdoid tumor and glioblastoma xenograft regrowth. *Neuro-Oncology, 18*(11), 1519–1528.
Hasselblatt, M., et al. (2014). SMARCA4-mutated atypical teratoid/rhabdoid tumors are associated with inherited germline alterations and poor prognosis. *Acta Neuropathologica, 128*(3), 453–456.
Hasselblatt, M., et al. (2020). Tyrosinase immunohistochemistry can be employed for the diagnosis of atypical teratoid/rhabdoid tumours of the tyrosinase subgroup (ATRT-TYR). *Neuropathology and Applied Neurobiology, 46*(2), 186–189.
Hilden, J. M., et al. (2004). Central nervous system atypical teratoid/rhabdoid tumor: results of therapy in children enrolled in a registry. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology, 22*(14), 2877–2884.
Ho, B., et al. (2020). Molecular subgrouping of atypical teratoid/rhabdoid tumors-a reinvestigation and current consensus. *Neuro-Oncology, 22*(5), 613–624.
Hooker, J. M., et al. (2010). Histone deacetylase inhibitor, MS-275, exhibits poor brain penetration: PK studies of [C]MS-275 using positron emission tomography. *ACS Chemical Neuroscience, 1*(1), 65–73.
Hou, H., Sun, D., & Zhang, X. (2019). The role of MDM2 amplification and overexpression in therapeutic resistance of malignant tumors. *Cancer Cell International, 19*, 216.
Howard, T. P., et al. (2019). MDM2 and MDM4 are therapeutic vulnerabilities in malignant rhabdoid tumors. *Cancer Research, 79*(9), 2404–2414.
Howard, T. P., et al. (2020). Rhabdoid tumors are sensitive to the protein-translation inhibitor homoharringtonine. *Clinical Cancer Research: an Official Journal of the American Association for Cancer Research, 26*(18), 4995–5006.
Hua, H., et al. (2019). Targeting mTOR for cancer therapy. *Journal of Hematology & Oncology, 12*(1), 71.
Hua, T., et al. (2024). Modeling human brain rhabdoid tumor by inactivating tumor suppressor genes in induced pluripotent stem cells. *Bioactive Materials, 31*, 136–150.
Hummel, T. R., et al. (2013). A pediatric phase 1 trial of vorinostat and temozolomide in relapsed or refractory primary brain or spinal cord tumors: A children's oncology group phase 1 consortium study. *Pediatric Blood & Cancer, 60*(9), 1452–1457.
Irving, M., et al. (2017). Engineering chimeric antigen receptor T-Cells for racing in solid tumors: Don't forget the fuel. *Frontiers in Immunology,* (8), 267.
Ishak, C. A., et al. (2016). An RB-EZH2 complex mediates silencing of repetitive DNA sequences. *Molecular Cell, 64*(6), 1074–1087.
Ishi, Y., et al. (2022). Therapeutic targeting of EZH2 and BET BRD4 in pediatric rhabdoid tumors. *Molecular Cancer Therapeutics, 21*(5), 715–726.
Jayabal, P., Ma, X., & Shiio, Y. (2021). EZH2 suppresses endogenous retroviruses and an interferon response in cancers. *Genes Cancer, 12*, 96–105.
Jin, M. Z., et al. (2018). Curaxin CBL0137 exerts anticancer activity via diverse mechanisms. *Frontiers in Oncology, 8*, 598.
Jin, Y. P., et al. (2014). Everolimus inhibits anti-HLA I antibody-mediated endothelial cell signaling, migration and proliferation more potently than sirolimus. *American Journal of Transplantation: Official Journal of the American Society of Transplantation and the American Society of Transplant Surgeons, 14*(4), 806–819.
Johann, P. D., et al. (2016). Atypical teratoid/rhabdoid tumors are comprised of three epigenetic subgroups with distinct enhancer landscapes. *Cancer Cell, 29*(3), 379–393.

Kannappan, S., et al. (2019). ATRT-15. Targeting LIN28 regulated pathways in novel therapeutics development for CNS atypical teratoid/rhabdoid tumor (CNS ATRT). *Neuro-Oncology, 21*(Supplement_2) ii66.
Katsumi, Y., et al. (2011). Sensitivity of malignant rhabdoid tumor cell lines to PD 0332991 is inversely correlated with p16 expression. *Biochemical and Biophysical Research Communications, 413*(1), 62–68.
Kerl, K., et al. (2013). The histone deacetylase inhibitor SAHA acts in synergism with fenretinide and doxorubicin to control growth of rhabdoid tumor cells. *BMC Cancer, 13*, 286.
Kinoshita, Y., et al. (2015). Glypican 3 expression in pediatric malignant solid tumors. *European Journal of Pediatric Surgery, 25*(1), 138–144.
Klaus, C. R., et al. (2017). Abstract 1944: Tazemetostat displays synergistic antiproliferative activity with backbone therapies in preclinical models of AT/RT and MRT. *Cancer Research,* 77(13_Supplement), 1944 1944.
Kleihues, P., et al. (2002). The WHO classification of tumors of the nervous system. *Journal of Neuropathology and Experimental Neurology, 61*(3), 215–225 discussion 226-9.
Kline, C., et al. (2024). TRLS-11. Pnoc005: Oncolytic measles virus for the treatment of children and young adults with recurrent medulloblastoma or atypical teratoid rhabdoid tumor. *Neuro-Oncology, 26*(Supplement_4) 0-0.
Knipstein, J. A., et al. (2012). Histone deacetylase inhibition decreases proliferation and potentiates the effect of ionizing radiation in atypical teratoid/rhabdoid tumor cells. *Neuro-Oncology, 14*(2), 175–183.
Knutson, S. K., et al. (2013). Durable tumor regression in genetically altered malignant rhabdoid tumors by inhibition of methyltransferase EZH2. *Proceedings of the National Academy of Sciences of the United States of America, 110*(19), 7922–7927.
Kohashi, K., et al. (2013). Glypican 3 expression in tumors with loss of SMARCB1/INI1 protein expression. *Human Pathology, 44*(4), 526–533.
Kolb, E. A., et al. (2008). Initial testing of dasatinib by the pediatric preclinical testing program. *Pediatric Blood & Cancer, 50*(6), 1198–1206.
Kordes, U., et al. (2014). Favorable outcome of patients affected by rhabdoid tumors due to rhabdoid tumor predisposition syndrome (RTPS). *Pediatric Blood & Cancer, 61*(5), 919–921.
Kramer, K., et al. (2022). Phase 1 study of intraventricular (131)I-omburtamab targeting B7H3 (CD276)-expressing CNS malignancies. *Journal of Hematology & Oncology, 15*(1), 165.
Laetsch, T. W., et al. (2024). Phase II study of samotolisib in children and young adults with tumors harboring phosphoinositide 3-kinase/mammalian target of rapamycin pathway alterations: Pediatric MATCH APEC1621D. *JCO Precision Oncology*(8), e2400258.
Lafay-Cousin, L., et al. (2012). Central nervous system atypical teratoid rhabdoid tumours: The Canadian paediatric brain tumour consortium experience. *European Journal of Cancer, 48*(3), 353–359.
Lanzi, C., et al. (2023). Targeting EZH2 in SMARCB1-deficient sarcomas: Advances and opportunities to potentiate the efficacy of EZH2 inhibitors. *Biochemical Pharmacology, 215*, 115727.
Larson, S. M., et al. (2015). Radioimmunotherapy of human tumours. *Nature Reviews. Cancer, 15*(6), 347–360.
Lee, R. S., et al. (2012). A remarkably simple genome underlies highly malignant pediatric rhabdoid cancers. *The Journal of Clinical Investigation, 122*(8), 2983–2988.
Lee, S., et al. (2011). Aurora a is a repressed effector target of the chromatin remodeling protein INI1/hSNF5 required for rhabdoid tumor cell survival. *Cancer Research, 71*(9), 3225–3235.

Lemmon, M. A., & Schlessinger, J. (2010). Cell signaling by receptor tyrosine kinases. *Cell, 141*(7), 1117–1134.
Leruste, A., et al. (2019). Clonally expanded T cells reveal immunogenicity of rhabdoid tumors. *Cancer Cell, 36*(6), 597–612.
Levy, C., Khaled, M., & Fisher, D. E. (2006). MITF: Master regulator of melanocyte development and melanoma oncogene. *Trends in Molecular Medicine, 12*(9), 406–414.
Li, N., et al. (2012). Lin-28 homologue a (LIN28A) promotes cell cycle progression via regulation of cyclin-dependent kinase 2 (CDK2), cyclin D1 (CCND1), and cell division cycle 25 homolog a (CDC25A) expression in cancer. *The Journal of Biological Chemistry, 287*(21), 17386–17397.
Lo Cascio, C., et al. (2023). Quisinostat is a brain-penetrant radiosensitizer in glioblastoma. *JCI Insight, 8*(22).
Lock, R., et al. (2017). Initial testing (stage 1) of the curaxin CBL0137 by the pediatric preclinical testing program. *Pediatric Blood & Cancer, 64*(4).
Louis, D. N., et al. (2016). The 2016 world health organization classification of tumors of the central nervous system: A summary. *Acta Neuropathologica, 131*(6), 803–820.
Lu, J. Q., et al. (2012). Immune cell infiltrates in atypical teratoid/rhabdoid tumors. *The Canadian Journal of Neurological, 39*(5), 605–612.
Ma, X. J., et al. (2020). Overall survival of primary intracranial atypical teratoid rhabdoid tumor following multimodal treatment: A pooled analysis of individual patient data. *Neurosurgical Review, 43*(1), 281–292.
Maachani, U. B., et al. (2020). B7-H3 as a prognostic biomarker and therapeutic target in pediatric central nervous system tumors. *Translational Oncology, 13*(2), 365–371.
Macy, M. E., et al. (2024). Palbociclib in solid tumor patients with genomic alterations in the cyclinD-cdk4/6-INK4a-Rb pathway: Results from national cancer Institute-Children's oncology group pediatric molecular analysis for therapy choice trial arm I (APEC1621I). *JCO Precision Oncology*(8), e2400418.
Mahalingam, D., et al. (2009). Targeting HSP90 for cancer therapy. *British Journal of Cancer, 100*(10), 1523–1529.
Malebranche, K., et al. (2023). ATRT-16. The PI3K inhibitor paxalisib combines synergistically with the mek inhibitor mirdametinib to target atypical teratoid/rhabdoid tumors. *Neuro-Oncology, 25*(Supplement_1), i4–i5.
Manfredi, M. G., et al. (2011). Characterization of alisertib (MLN8237), an investigational small-molecule inhibitor of aurora a kinase using novel in vivo pharmacodynamic assays. *Clinical Cancer Research: an Official Journal of the American Association for Cancer Research, 17*(24), 7614–7624.
Meel, M. H., et al. (2020). MEK/MELK inhibition and blood-brain barrier deficiencies in atypical teratoid/rhabdoid tumors. *Neuro-Oncology, 22*(1), 58–69.
Merk, D. J., et al. (2024). Functional screening reveals genetic dependencies and diverging cell cycle control in atypical teratoid rhabdoid tumors. *Genome Biology, 25*(1), 301.
Metselaar, D. S., et al. (2024). Gemcitabine therapeutically disrupts essential SIRT1-mediated p53 repression in atypical teratoid/rhabdoid tumors. *Cell Reports Medicine, 5*(9), 101700.
Moreno, N., et al. (2017). Combined BRD4 and CDK9 inhibition as a new therapeutic approach in malignant rhabdoid tumors. *Oncotarget, 8*(49), 84986–84995.
Morin, A., et al. (2020). Proteasome inhibition as a therapeutic approach in atypical teratoid/rhabdoid tumors. *Neuro-Oncology Advances, 2*(1), vdaa051.
Mossé, Y. P., et al. (2019). A phase II study of alisertib in children with Recurrent/refractory solid tumors or leukemia: Children's oncology group phase I and pilot consortium (ADVL0921). *Clinical Cancer Research: an Official Journal of the American Association for Cancer Research, 25*(11), 3229–3238.

Mossé, Y. P., et al. (2012). Pediatric phase I trial and pharmacokinetic study of MLN8237, an investigational oral selective small-molecule inhibitor of aurora kinase A: A children's oncology group phase I consortium study. *Clinical Cancer Research: an Official Journal of the American Association for Cancer Research, 18*(21), 6058–6064.

Msaouel, P., et al. (2019). Phase II trial of ixazomib combined with gemcitabine and doxorubicin in patients with SMARCB1-deficient kidney malignancies. *Journal of Clinical Oncology, 37*(7_suppl) TPS678-TPS678.

Muscat, A., et al. (2016). Low-dose histone deacetylase inhibitor treatment leads to tumor growth arrest and multi-lineage differentiation of malignant rhabdoid tumors. *Clinical Cancer Research: an Official Journal of the American Association for Cancer Research, 22*(14), 3560–3570.

Myers, R. M., et al. (2007). Preclinical pharmacology and toxicology of intravenous MV-NIS, an oncolytic measles virus administered with or without cyclophosphamide. *Clinical Pharmacology and Therapeutics, 82*(6), 700–710.

Nakata, S., et al. (2020). ATRT-17. Targeting glutamine metabolism lowers methylation potencials in AT/RT and synergize with tazemetostat. *Neuro-Oncology, 22*(Supplement_3) iii279-iii279.

Nemes, K., et al. (2021). Clinical and genetic risk factors define two risk groups of extracranial malignant rhabdoid tumours (eMRT/RTK). *European Journal of Cancer, 142*, 112–122.

Nemes, K., et al. (2018). The extraordinary challenge of treating patients with congenital rhabdoid tumors—a collaborative european effort. *Pediatric Blood & Cancer, 65*(6), e26999.

Nicolaides, T., et al. (2010). High-dose chemotherapy and autologous stem cell rescue for atypical teratoid/rhabdoid tumor of the central nervous system. *Journal of Neuro-Oncology, 98*(1), 117–123.

Nigg, E. A. (2001). Mitotic kinases as regulators of cell division and its checkpoints. *Nature Reviews. Molecular Cell Biology, 2*(1), 21–32.

Nikonova, A. S., et al. (2013). Aurora a kinase (AURKA) in normal and pathological cell division. *Cellular and Molecular Life Sciences: CMLS, 70*(4), 661–687.

Novak, O., et al. (2023). ATRT-12. Hyperactivating the integrated stress response with proteasome inhibition in AT/RT. *Neuro-Oncology, 25*(Supplement_1), i3–i4.

Novotná, K., et al. (2024). Therapeutic resurgence of 6-diazo-5-oxo-l-norleucine (Don) through tissue-targeted prodrugs. *Advances in Pharmacological and Pharmaceutical Sciences, 100*, 157–180.

Oka, H., & Scheithauer, B. W. (1999). Clinicopathological characteristics of atypical teratoid/rhabdoid tumor. *Neurologia Medico-Chirurgica, 39*(7), 510–517 discussion 517-8.

O'Leary, B., Finn, R. S., & Turner, N. C. (2016). Treating cancer with selective CDK4/6 inhibitors. *Nature Reviews Clinical Oncology, 13*(7), 417–430.

Olsauskas-Kuprys, R., Zlobin, A., & Osipo, C. (2013). Gamma secretase inhibitors of notch signaling. *OncoTargets and Therapy, 6*, 943–955.

Olson, T. A., et al. (1995). Successful treatment of disseminated central nervous system malignant rhabdoid tumor. *Journal of Pediatric Hematology/Oncology: Official Journal of the American Society of Pediatric Hematology/Oncology, 17*(1), 71–75.

Ortiz, M. V., et al. (2019). Immunotherapeutic targeting of GPC3 in pediatric solid embryonal tumors. *Frontiers in Oncology, 9*, 108.

Oruetxebarria, I., et al. (2004). P16INK4a is required for hSNF5 chromatin remodeler-induced cellular senescence in malignant rhabdoid tumor cells. *The Journal of Biological Chemistry, 279*(5), 3807–3816.

Ostrom, Q. T., et al. (2014). The descriptive epidemiology of atypical teratoid/rhabdoid tumors in the United States, 2001-2010. *Neuro-Oncology, 16*(10), 1392–1399.

Paassen, I., et al. (2023). Atypical teratoid/rhabdoid tumoroids reveal subgroup-specific drug vulnerabilities. *Oncogene, 42*(20), 1661–1671.
Packer, R. J., et al. (2002). Atypical teratoid/rhabdoid tumor of the central nervous system: Report on workshop. *Journal of Pediatric Hematology/Oncology: Official Journal of the American Society of Pediatric Hematology/Oncology, 24*(5), 337–342.
Panwalkar, P., et al. (2020). SWI/SNF complex heterogeneity is related to polyphenotypic differentiation, prognosis, and immune response in rhabdoid tumors. *Neuro-Oncology, 22*(6), 785–796.
Parato, K. A., et al. (2005). Recent progress in the battle between oncolytic viruses and tumours. *Nature Reviews. Cancer, 5*(12), 965–976.
Park, S.-Y., & Kim, J.-S. (2020). A short guide to histone deacetylases including recent progress on class II enzymes. *Experimental & Molecular Medicine, 52*(2), 204–212.
Parkhurst, A., et al. (2022). Dual mTORC1/2 inhibition compromises cell defenses against exogenous stress potentiating obatoclax-induced cytotoxicity in atypical teratoid/rhabdoid tumors. *Cell Death & Disease, 13*(4), 410.
Pauck, D., et al. (2025). An in vitro pharmacogenomic approach reveals subtype-specific therapeutic vulnerabilities in atypical teratoid/rhabdoid tumors (AT/RT). *Pharmacological Research: the Official Journal of the Italian Pharmacological Society, 213*, 107660.
Pearson, A. D., et al. (2021). Bromodomain and extra-terminal inhibitors-A consensus prioritisation after the paediatric strategy forum for medicinal product development of epigenetic modifiers in children-accelerate. *European Journal of Cancer, 146*, 115–124.
Pham, K., et al. (2021). Novel glutamine antagonist JHU395 suppresses MYC-driven medulloblastoma growth and induces apoptosis. *Journal of Neuropathology and Experimental Neurology, 80*(4), 336–344.
Pinto, E. M., et al. (2018). Malignant rhabdoid tumors originating within and outside the central nervous system are clinically and molecularly heterogeneous. *Acta Neuropathologica, 136*(2), 315–326.
Popovic, R., & Licht, J. D. (2012). Emerging epigenetic targets and therapies in cancer medicine. *Cancer Discovery, 2*(5), 405–413.
Qian, S., et al. (2022). The role of BCL-2 family proteins in regulating apoptosis and cancer therapy. *Frontiers in Oncology, 12*, 985363.
Quinn, T. J., et al. (2019). Trimodality therapy for atypical teratoid/rhabdoid tumor is associated with improved overall survival: A surveillance, epidemiology, and end results analysis. *Pediatric Blood & Cancer, 66*(12), e27969.
Reddy, A., et al. (2021). ATRT-04. Correlation of clinicopathologic features and cumulative incidence of relapse for patients with atypical teratoid rhabdoid tumor on ACNS0333: A report from the children's oncology group. *Neuro-Oncology, 23*(Supplement_1), i1.
Reddy, A. (2003). Treatment of atypical teratoid/rhabdoid tumors (AT/RT) of the central nervous system with surgery, intensive chemotherapy, and 3-D conformal radiation. *Children's Oncology Group ACNS, 0333*, 9–16.
Reddy, A. T., et al. (2020). Efficacy of high-dose chemotherapy and three-dimensional conformal radiation for atypical teratoid/rhabdoid tumor: A report from the children's oncology group trial ACNS0333. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology, 38*(11), 1175–1185.
Roberts, C., & Biegel, J. (2009). The role of SMARCB1/INI1 in the development of rhabdoid tumors. *Cancer Biology & Therapy, 8*(5), 412–416.
Robinson, G. W., et al. (2024). TRLS-16. Results from SJDAWN: A ST jude children's research Hospital phase 1 study evaluating molecularly driven doublet therapies for all children with refractory or recurrent central nervous system (cns) malignant neoplasms and young adults with SHH medulloblastoma. *Neuro-Oncology, 26*(Supplement_4), 0 0.

Rorke, L. B., Packer, R., & Biegel, J. (1995). Central nervous system atypical teratoid/rhabdoid tumors of infancy and childhood. *Journal of Neuro-Oncology, 24*(1), 21–28.
Rorke, L. B., Packer, R. J., & Biegel, J. A. (1996). Central nervous system atypical teratoid/rhabdoid tumors of infancy and childhood: Definition of an entity. *Journal of Neurosurgery, 85*(1), 56–65.
Rubens, J. A., et al. (2017). The TORC1/2 inhibitor TAK228 sensitizes atypical teratoid rhabdoid tumors to cisplatin-induced cytotoxicity. *Neuro-Oncology, 19*(10), 1361–1371.
Sadelain, M., Brentjens, R., & Rivière, I. (2013). The basic principles of chimeric antigen receptor design. *Cancer Discovery, 3*(4), 388–398.
Safaei, S., et al. (2021). DIMEimmune: Robust estimation of infiltrating lymphocytes in CNS tumors from DNA methylation profiles. *Oncoimmunology, 10*(1), 1932365.
Schneppenheim, R., et al. (2010). Germline nonsense mutation and somatic inactivation of SMARCA4/BRG1 in a family with rhabdoid tumor predisposition syndrome. *American Journal of Human Genetics, 86*(2), 279–284.
Schramm, J., et al. (2025). Polyamine inhibition with DFMO: Shifting the paradigm in neuroblastoma therapy. *Journal of Clinical Medicine, 14*(4).
SEER, SEER 22 Incidence 2017–2021 & U.S. Mortality 2018–2022, Ages 0–19. 2023.
Shahab, S., et al. (2020). MEK inhibition suppresses growth of atypical teratoid/rhabdoid tumors. *Journal of Neuropathology and Experimental Neurology, 79*(7), 746–753.
Singh, A., et al. (2013). Profiling pathway-specific novel therapeutics in preclinical assessment for central nervous system atypical teratoid rhabdoid tumors (CNS ATRT): Favorable activity of targeting EGFR- ErbB2 signaling with lapatinib. *Molecular Oncology, 7*(3), 497–512.
Slavc, I., et al. (2014). Atypical teratoid rhabdoid tumor: Improved long-term survival with an intensive multimodal therapy and delayed radiotherapy. The medical university of Vienna experience 1992-2012. *Cancer Medicine, 3*(1), 91–100.
Sredni, S. T., et al. (2017). A functional screening of the kinome identifies the Polo-like kinase 4 as a potential therapeutic target for malignant rhabdoid tumors, and possibly, other embryonal tumors of the brain. *Pediatric Blood & Cancer, 64*(11).
Steinbügl, M., et al. (2021). Clinical evidence for a biological effect of epigenetically active decitabine in relapsed or progressive rhabdoid tumors. *Pediatric Blood & Cancer, 68*(12), e29267.
Strother, D. R., et al. (2013). Benefit from prolonged dose-intensive chemotherapy for infants with malignant brain tumors is restricted to patients with ependymoma: A report of the pediatric oncology group randomized controlled trial 9233/34. *Neuro-Oncology, 16*(3), 457–465.
Studebaker, A. W., et al. (2015). Oncolytic measles virus efficacy in murine xenograft models of atypical teratoid rhabdoid tumors. *Neuro-Oncology, 17*(12), 1568–1577.
Studebaker, A. W., et al. (2017). Oncolytic herpes virus rRp450 shows efficacy in orthotopic xenograft group 3/4 medulloblastomas and atypical teratoid/rhabdoid tumors. *Molecular Therapy Oncolytics, 6*, 22–30.
Sung, K. W., et al. (2016). Tandem high-dose chemotherapy and autologous stem cell transplantation for atypical teratoid/rhabdoid tumor. *Cancer Research and Treatment, 48*(4), 1408–1419.
Tekautz, T. M., et al. (2005). Atypical teratoid/rhabdoid tumors (ATRT): Improved survival in children 3 years of age and older with radiation therapy and high-dose alkylator-based chemotherapy. *Journal of Clinical Oncology, 23*(7), 1491–1499.
Theruvath, J., et al. (2020). Locoregionally administered B7-H3-targeted CAR t cells for treatment of atypical teratoid/rhabdoid tumors. *Nature Medicine, 26*(5), 712–719.
Thiemann, M., et al. (2012). In vivo efficacy of the histone deacetylase inhibitor suberoylanilide hydroxamic acid in combination with radiotherapy in a malignant rhabdoid tumor mouse model. *Radiation Oncology, 7*(1), 52.

Tief, K., et al. (1996). Tyrosinase is a new marker for cell populations in the mouse neural tube. *Developmental Dynamics: an Official Publication of the American Association of Anatomists, 205*(4), 445–456.
Torchia, J., et al. (2016). Integrated (epi)-genomic analyses identify subgroup-specific therapeutic targets in CNS rhabdoid tumors. *Cancer Cell, 30*(6), 891–908.
Toson, B., et al. (2022). Targeting Akt/PKB in pediatric tumors: A review from preclinical to clinical trials. *Pharmacological Research: the Official Journal of the Italian Pharmacological Society, 183*, 106403.
Townsend, P. A., et al. (2021). BH3-mimetics: Recent developments in cancer therapy. *Journal of Experimental & Clinical Cancer Research: CR, 40*(1), 355.
Tran, H. M., et al. (2020). Upregulation of protein synthesis and proteasome degradation confers sensitivity to proteasome inhibitor bortezomib in myc-atypical teratoid/rhabdoid tumors. *Cancers (Basel), 12*(3).
Tran, Q. T., et al. (2023b). DNA-methylation subgroups carry no prognostic significance in ATRT-SHH patients in clinical trial cohorts. *Acta Neuropathologica, 146*(3), 543–545.
Tran, S., et al. (2023a). Current advances in immunotherapy for atypical teratoid rhabdoid tumor (ATRT). *Neuro-oncology Practice, 10*(4), 322–334.
Tsikitis, M., et al. (2005). Genetic ablation of cyclin D1 abrogates genesis of rhabdoid tumors resulting from Ini1 loss. *Proceedings of the National Academy of Sciences of the United States of America, 102*(34), 12129–12134.
Turner, J. G., Dawson, J., & Sullivan, D. M. (2012). Nuclear export of proteins and drug resistance in cancer. *Biochemical Pharmacology, 83*(8), 1021–1032.
Underiner, R. M., et al. (2020). Meta-Analysis of treatment modalities in metastatic atypical teratoid/rhabdoid tumors in children. *Pediatric Neurology, 108*, 106–112.
Upadhyaya, S. A., et al. (2018). Malignant progression of a peripheral nerve sheath tumor in the setting of rhabdoid tumor predisposition syndrome. *Pediatric Blood & Cancer, 65*(7), e27030.
Upadhyaya, S. A., et al. (2023). Phase II study of alisertib as a single agent for treating recurrent or progressive atypical teratoid/rhabdoid tumor. *Neuro-Oncology, 25*(2), 386–397.
Upadhyaya, S. A. (2020). Relevance of the type and timing of radiation therapy to the outcomes reported in the ACNS0333 trial for atypical teratoid/rhabdoid tumors. *Journal of Clinical Oncology, 38*(28) 3352-3352.
Upadhyaya, S. A., et al. (2021). Relevance of molecular groups in children with newly diagnosed atypical teratoid rhabdoid tumor: Results from prospective st. Jude multi-institutional trials. *Clinical Cancer Research: an Official Journal of the American Association for Cancer Research, 27*(10), 2879–2889.
van Gool, S. W., et al. (2016). Immunotherapy in atypical teratoid-rhabdoid tumors: Data from a survey of the HGG-Immuno group. *Cytotherapy, 18*(9), 1178–1186.
Venkataraman, S., et al. (2012). Targeting aurora kinase a enhances radiation sensitivity of atypical teratoid rhabdoid tumor cells. *Journal of Neuro-Oncology, 107*(3), 517–526.
von Hoff, K., et al. (2011). Frequency, risk-factors and survival of children with atypical teratoid rhabdoid tumors (AT/RT) of the CNS diagnosed between 1988 and 2004, and registered to the German HIT database. *Pediatric Blood & Cancer, 57*(6), 978–985.
Wang, D., et al. (2018). Targeting EZH2 reprograms intratumoral regulatory T cells to enhance cancer immunity. *Cell Reports, 23*(11), 3262–3274.
Wang, S. Z., et al. (2019). Unbiased metabolic profiling predicts sensitivity of high MYC-expressing atypical teratoid/rhabdoid tumors to glutamine inhibition with 6-Diazo-5-Oxo-L-norleucine. *Clinical Cancer Research: an Official Journal of the American Association for Cancer Research, 25*(19), 5925–5936.
Wang, W., et al. (2024). MDM2 inhibitors for cancer therapy: The past, present, and future. *Pharmacological Reviews, 76*(3), 414–453.

Wang, X., et al. (2017). SMARCB1-mediated SWI/SNF complex function is essential for enhancer regulation. *Nature Genetics, 49*(2), 289–295.
Weinblatt, M., & Kochen, J. (1992). Rhabdoid tumor of the central nervous system. *Medical and Pediatric Oncology, 20*(3), 258.
Weingart, M. F., et al. (2015). Disrupting LIN28 in atypical teratoid rhabdoid tumors reveals the importance of the mitogen activated protein kinase pathway as a therapeutic target. *Oncotarget, 6*(5), 3165–3177.
Wetmore, C., et al. (2015). Alisertib is active as single agent in recurrent atypical teratoid rhabdoid tumors in 4 children. *Neuro-Oncology, 17*(6), 882–888.
Wilson, B. G., et al. (2010). Epigenetic antagonism between polycomb and SWI/SNF complexes during oncogenic transformation. *Cancer Cell, 18*(4), 316–328.
Woehrer, A., et al. (2010). Incidence of atypical teratoid/rhabdoid tumors in children: a population-based study by the Austrian brain tumor registry, 1996-2006. *Cancer, 116*(24), 5725–5732.
Wong, J. P., et al. (2016). Dual targeting of PDGFRα and FGFR1 displays synergistic efficacy in malignant rhabdoid tumors. *Cell Reports, 17*(5), 1265–1275.
Wood, P., et al. (2020). ATRT-08. A phase II study of continuous low dose panobinostat in paediatric patients with malignant rhabdoid tumors/atypical teratoid rhabdoid tumors. *Neuro-Oncology, 22*(Supplement_3), iii277.
Xu, D., Grishin, N. V., & Chook, Y. M. (2012). NESdb: A database of NES-containing CRM1 cargoes. *Molecular Biology of the Cell, 23*(18), 3673–3676.
Xu, W. S., Parmigiani, R. B., & Marks, P. A. (2007). Histone deacetylase inhibitors: Molecular mechanisms of action. *Oncogene, 26*(37), 5541–5552.
Xue, Y., et al. (2020). SMARCB1 loss induces druggable cyclin D1 deficiency via upregulation of MIR17HG in atypical teratoid rhabdoid tumors. *The Journal of Pathology, 252*(1), 77–87.
Yang, F., et al. (2019). Next-generation of selective histone deacetylase inhibitors. *RSC Advances, 9*(34), 19571–19583.
Yang, W. C., et al. (2020). Effect of early radiotherapy initiation and high-dose chemotherapy on the prognosis of pediatric atypical teratoid rhabdoid tumors in different age groups. *Journal of Neuro-Oncology, 147*(3), 619–631.
Yin, D., et al. (2007). Suberoylanilide hydroxamic acid, a histone deacetylase inhibitor: Effects on gene expression and growth of glioma cells in vitro and in vivo. *Clinical Cancer Research: an Official Journal of the American Association for Cancer Research, 13*(3), 1045–1052.
Zaky, W., et al. (2014). Intensive induction chemotherapy followed by myeloablative chemotherapy with autologous hematopoietic progenitor cell rescue for young children newly-diagnosed with central nervous system atypical teratoid/rhabdoid tumors: The head start III experience. *Pediatric Blood & Cancer, 61*(1), 95–101.
Zhang, Z. K., et al. (2002). Cell cycle arrest and repression of cyclin D1 transcription by INI1/hSNF5. *Molecular and Cellular Biology, 22*(16), 5975–5988.
Zhou, J., Ng, S. B., & Chng, W. J. (2013). LIN28/LIN28B: An emerging oncogenic driver in cancer stem cells. *The International Journal of Biochemistry & Cell Biology, 45*(5), 973–978.
Zhu, H., et al. (2011). The Lin28/let-7 axis regulates glucose metabolism. *Cell, 147*(1), 81–94.