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Publication Date
2023-03-01

DOI
10.1016/j.neo.2023.100880

Peer reviewed

Neoplasia 37 (2023) 100880

Contents lists available at ScienceDirect

Neoplasia

journal homepage: www.elsevier.com/locate/neo

Recent progress and novel approaches to treating atypical teratoid rhabdoid tumor ☆

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ARTICLE INFO

Keywords:
INI1
MYC
epigenetics
adaptive
clinical trial
mTOR
MEK

ABSTRACT

Atypical teratoid rhabdoid tumors (AT/RT) are malignant central nervous system (CNS) tumors that occur mostly in young children and have historically carried a very poor prognosis. While recent clinical trial results show that this tumor is curable, outcomes are still poor compared to other central nervous system embryonal tumors. We here review prior AT/RT clinical trials and highlight promising pre-clinical results that may inform novel clinical approaches to this aggressive cancer.

Introduction

While only representing 3% of all pediatric CNS tumors, AT/RT is the most common malignant CNS tumor in children less than one year of age and represents 20% of CNS tumors in children less than three years of age [1–4],. The World Health Organization recognized AT/RT as a formal diagnostic category in 2000 [5,6]. Bi-allelic loss of function mutations in the *SMARCB1* gene define the majority of cases of AT/RT [7–9]. The remaining cases carry loss of function mutations in the *SMARCA4* gene [10]. Although the morphologic appearance of AT/RT varies significantly, the loss of INI1 (*SMARCB1)* or BRG1 (*SMARCA4)* by immunohistochemical staining allows for rapid histologic diagnosis [10,11]. Approximately one-third of patients with AT/RT have an underlying germline *SMARCB1* alteration resulting in rhabdoid tumor predisposition syndrome, carrying a risk of multiple CNS and non-CNS rhabdoid tumors [12]. Although AT/RT harbor no recurrent genetic alterations outside of *SMARCB1* and *SMARCA4*, AT/RT can be grouped into three consensus molecular subgroups defined by DNA methylation and RNA expression [13–15].

Following the recognition of AT/RT as a distinct entity, disease specific approaches using intensive, multimodal therapies have led to improved survival outcomes [16–18]. Toxicity of current treatment options is high [16,17,19-21] and there is still much to understand about how molecular subgroups and other prognostic factors may be used in future clinical trials to stratify treatment. Novel therapies and innovative approaches to clinical trial design are potential opportunities to continue to improve outcomes for these patients.

Methods

We performed a search of PubMed using the following combinations of keywords: "teratoid," "rhabdoid," and "therapeutic." This retrieved a total of 347 articles that were reviewed for applicability for AT/RT. We prioritized for inclusion prospective clinical trials including AT/RT patients as well as large registry data. Abstracts from recent scientific meetings were also included if reporting results of a recently completed or ongoing clinical trial including AT/RT patients. In addition, we prioritized for inclusion publications describing novel therapeutics that demonstrated efficacy in animal models. We obtained additional references from initially selected articles.

Discussion

Completed trials for newly diagnosed AT/RT patients

Due to the rarity of this tumor type, the majority of historical data on treatment of AT/RT arises from retrospective reviews and small

☆ Funding support: National Cancer Institute Core Grant to the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center (P30CA006973) (ER and JR).
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https://doi.org/10.1016/j.neo.2023.100880
Received 23 August 2022; Received in revised form 12 January 2023; Accepted 23 January 2023

Table 1
Prospective Clinical Trials in AT/RT

Protocol	Number of Patients (n)	Chemotherapy Regimen	Timing of Radiation: (n)	Outcomes
CCG921	28	Regimen A: VCR, CDDP, CPM, ETOP x 5 cycles Regimen B: VCR, CBP, IFOS, ETOP x 5 cycles Maintenance: VCR, ETOP, CBP, ETOP x 8 cycles	Adjuvant: 2 Salvage: 9	5-yr EFS: 14%±7% 5-yr OS: 29%±9%
Head Start III	19	Induction Cycle 1, 3, 5: CDDP, VCR, ETOP, CPM, HDMTX Induction Cycle 2, 4: TEM, ETOP, VCR, CPM Consolidation with HDCT: CBP, Thiotepa, ETOP	Salvage: 5	3-yr EFS: 21%±9% 3-yr OS: 26%±10%
DFCI IRS-III	20	VCR, ACT-D, CPM, CDDP, DOX, TEM IT chemotherapy: MTX, HCT, ARA-C	Adjuvant: 15	2-yr PFS: 53%±13% 2-yr OS: 70%±10%
ACNS0333	65	Induction: MTX, VCR, ETOP, CPM, CDDP x 2 cycles Consolidation with HDCT: CBP, Thiotepa, ETOP x 3 cycles	Adjuvant: 42	4-yr EFS: 37% 4-yr OS: 43%
SJYC07	52	IR: Induction: HDMTX, VCR, CPM, CDDP x 4 cycles Maintenance: PO CTX/TOPO alternating with PO ETOP HR: Induction: HDMTX, VCR, CPM, CDDP, VBL x 4 cycles Consolidation: CPM/TOPO x 2 cycles Maintenance: PO CPM/TOPO alternating with PO ETOP	Adjuvant: 34 (IR only)	IR: 5-yr PFS: 31.4%±9.2% 5-yr OS: 43.9%±9.5% HR: 5yr PFS and OS: 0%
SJMB03	22	CDDP, VCR, CPM followed by PBSC x 4 cycles	Adjuvant: 22	AR: 5-yr PFS: 72.7%±12.7% 5-yr OS: 81.8% ±11.0% HR: 5-yr PFS and OS: 18.2%±9.5%

Abbreviations: ACT-D, dactinomycin; AR, average risk; ARA-C, cytarabine; CBP, carboplatin; CDDP, cisplatin; CPM, cyclophosphamide; DFCI, Dana-Farber Cancer Institute; DOX, doxorubicin; EFS, event free survival; ETOP, etoposide; HCT, hydrocortisone; HDCT, high dose chemotherapy; HDMTX, high dose methotrexate; HR; high risk; IFOS, ifosfamide; IR, intermediate risk; IRS, Intergroup Rhabdomyosarcoma Study; MTX, methotrexate; OS, overall survival; PBSC, peripheral blood stem cells; PO, oral; TEM, temozolomide; TOPO, topotecan; VCR, vincristine;

studies. Though historical "baby" protocols for young children with CNS tumors included patients with AT/RT, only recently have larger, prospective studies been completed that were designed specifically for AT/RT (Table 1).

CCG9921

One early study through the Children's Cancer Group, CCG9921, randomized subjects to one of two intensive platinum-based multi-agent chemotherapy regimens, followed by maintenance chemotherapy with the goal of avoiding radiation therapy [22]. This study was designed for malignant brain tumors of varying histologies in infants < 36 months of age and included 28 AT/RT patients. Eleven of the 28 AT/RT patients received radiation therapy on study, with nine of those receiving irradiation at the time of disease recurrence or progression. Patients with AT/RT experienced worse outcomes compared to infants with tumors of other histologies, and the 5-year event free survival (EFS) and overall survival (OS) were 14% and 29%, respectively, which was not improved compared to historical controls.

Head Start

Efforts to intensify chemotherapy to avoid radiation therapy in these young patients continued with the Head Start protocols, where sequential prospective studies included 13 patients on Head Start 1 and II and 19 patients on Head Start III [19,23]. After initial surgical resection, patients received five cycles of multi-agent chemotherapy followed by one cycle of high dose chemotherapy (HDC) with autologous stem cell rescue. On Head Start III, owing to toxicity and progressive disease in patients during induction, only four of 19 patients completed all five cycles of chemotherapy and only three proceed to consolidation. The 3-year EFS and OS were 21% and 26%, respectively.

DFCI-AT/RT

The first prospective trial designed specifically for AT/RT patients, a multi-institutional trial (NCT00084838) led by Dana-Farber Cancer Institute (DFCI), consisted of a chemotherapy backbone based on the Intergroup Rhabdomyosarcoma Group-III protocol for rhabdomyosarcoma with parameningeal extension. Upfront surgical resection was followed by 51 weeks of multi-agent systemic anthracycline-based chemotherapy with concurrent intrathecal chemotherapy. After the initial six weeks of induction chemotherapy, patients received radiation with concurrent chemotherapy. Patients with M0 disease received focal radiation therapy. Patients older than three years with M+ disease received craniospinal irradiation (CSI). Survival was encouraging with 2-year progression free survival (PFS) and OS of 53% and 70%, respectively. Extent of resection was prognostic by univariate analyses, with patients who achieved gross total resection demonstrating a 2-year OS of 91%. Tumor location also influenced OS, with posterior fossa location being favorable over supratentorial location. As expected, this intensive regimen was associated with frequent grade 3-4 toxicities. There was one case of toxic death during induction, one case of transverse myelitis that required therapy cessation and two patients that experienced radiation recall, one near therapy completion and another following it.

EU-RHAB

The European Registry for rhabdoid tumors (EU-RHAB) has published results on 31 patients uniformly treated with systemic and intrathecal chemotherapy [24]. Additional therapy modalities included radiotherapy in 23 patients, HDCT in 8 patients and additional maintenance chemotherapy for 17 patients. For the entire study cohort, the reported 6-year event-free survival (EFS) and OS were 46% and 45%, respectively. Age > 3 years and metastatic status were found to be prognostic factors of statistical significance in this study. In addition, the ability to reach a complete remission and the incorporation of radiotherapy were statistically significant positive prognostic factors. Major toxicities reported in this study included one treatment related death secondary to VP-shunt failure and three instances of treatment discontinuation due to pneumonia, recurrent infections and methotrexate induced leukoencephalopathy. In a more recent publication from the EU-RHAB group, results from 143 patients are reported. Outcomes reported for this larger cohort were 5-year EFS and OS of 31% and 35%, respectively. Age re-

mained an important determinant of outcome, as did metastatic disease and synchronous tumors. Methylation profiling was available for 84/143 patients, showing a survival advantage for patients with ATRT-TYR subgroup when compared to non-TYR ATRT [18].

ACNS0333

The largest prospective trial specifically for patients with AT/RT, the Children's Oncology Group (COG) trial ACNS0333, combined two cycles of intensive multi-agent chemotherapy including high dose methotrexate with three tandem cycles of HDC with autologous stem cell rescue [17]. Second-look surgery was encouraged prior to consolidation. Timing and extent of radiation therapy ware based on age and extent of disease at presentation. Sixty-five evaluable patients with AT/RT were enrolled on study and two year EFS was 42%. Four-year EFS and OS were 37% and 43% respectively. Approximately a third of patients had disease relapse on treatment with a cumulative incidence of relapse (CIR) of 22% at 6 months and 41% at one year [25]. Age at diagnosis, location, extent of initial resection, and presence of metastatic disease were not found to be prognostic for EFS, OS, or CIR. Patients with *SMARCB1* germline mutation or tumors that involved the infratentorial and supratentorial compartments simultaneously had a worse outcome, but the number of patients in each category was too small to reach significance. Main toxicities of ACNS0333 included myelosuppression and infectious complications. There were four treatment-related deaths: one from sepsis during induction, one from pulmonary fibrosis, and two from CNS necrosis. Of note, the study was amended to decrease the risk of pulmonary toxicity, with no further cases following these changes. Retrospective molecular subtyping was performed on tumors of children enrolled on this study, and each was identified as one of the 3 molecular subtypes (TYR, SHH and MYC) previously reported [13,14]. While not powered to evaluate the effect of subtype on outcome, it is notable that patients with SHH subtype had a 6-month EFS of 100%. Thirty-four of the 40 patients who received RT had focal RT only. Patients with no evidence of disease at the time of radiation had a 4-year OS of 79% (Reddy, personal communication). There was no difference in EFS/OS/CIR based on the order of radiation and consolidation, but there was increased neurotoxicity when radiation was administered between induction and consolidation. The investigators recommend that patients receive radiation after consolidation on future trials that use this backbone.

SJYC07 and SJMB03

The St. Jude Children's Research Hospital prospective risk-adapted trials SJYC07 and SJMB03 also showed that multimodal therapy can achieve long-term survival in some children with AT/RT [26]. The SJYC07 cohort included 55 infants less than 36 months of age and stratified patients into intermediate risk and high risk based on the absence or presence of metastatic disease. After maximal safe upfront resection, intermediate risk patients were treated with 4 cycles of multi-agent induction chemotherapy followed by focal radiation and maintenance chemotherapy for 24 weeks. Second-look surgery was performed in patients with residual disease after 2-4 cycles of induction chemotherapy. High-risk patients received 4 cycles of induction chemotherapy similar to intermediate risk patients but with the addition of vinblastine, followed by consolidation with 2 cycles of cyclophosphamide and topotecan, and oral maintenance therapy. Craniospinal irradiation (CSI) was optional for patients who were ≥ 3 years of age at the end of induction. The 5-year PFS and OS for intermediate risk patients were 31% and 44%, respectively. Unfortunately, 5-year PFS and OS for high risk patients was 0%. SJMB03 enrolled 22 children ≥ 36 months of age and stratified patients to average risk (M0 and < 1.5cm^2 of residual tumor) or high risk (M+ or ≥ 1.5cm^2 of residual tumor). All patients received risk-adapted CSI with boost to primary and metastatic sites. CSI was followed by 4 cycles of multi-agent chemotherapy with peripheral blood stem cell support. Five-year PFS and OS for average-risk patients were 73% and 82%, respectively. For high-risk patients, 5-year PFS and OS were 18%. There was no evidence that presence of a germline *SMARCB1* or *SMARCA4* mutation influenced outcome in these cohorts. For both SJYC07 and SJMB03, the most common toxicity was febrile neutropenia, with one reported case of death following febrile neutropenia and a respiratory infection. Molecular subtypes were retrospectively evaluated and suggest that infants with TYR subgroup AT/RT treated on SJYC07 had improved outcomes compared to those with SHH or MYC subgroups. However, outcomes for patients without metastases at diagnosis were similar between the different AT/RT molecular subgroups.

Impact of extent of resection

Evaluation of these clinical trials shows a mixed picture of the impact of GTR on survival. While the DFCI trial showed in univariate analysis that GTR significantly improved survival [27], in the ACNS0333 cohort GTR vs STR vs biopsy did not affect survival [17]. Similarly, in the European EU-RHAB AT/RT cohort, extent of resection did not significantly affect outcome [24]. In the St. Jude series, in the SJYC07 cohort of children less than 3 years, second-look surgery was encouraged to achieve a GTR. In this cohort, outcomes did not differ by extent of resection. In the SJMB03 older cohort of children greater than 3 years of age, the extent of resection was incorporated into risk stratification, and patients with greater than 1.5 cm^2 of residual tumor were classified as high risk. This group, which also included patients with metastatic disease at outset, did significantly worse than average risk patients [26].

Influence of epigenetic subtype

There are 3 consensus epigenetic subgroups of AT/RT: TYR, SHH, and MYC [3,28-30]. These subgroups differ in gene expression profile, location, method of inactivating *SMARCB1* and in susceptibility to targeted therapy [29–31]. In the ACNS0333 cohort, there was a trend towards increasing risk of relapse in patients with the MYC subgroup, but this has not reached statistical significance [25]. A close examination of the SJYC07 data shows that TYR patients were less likely to be metastatic at onset, and when only M0 patients were included, there was no difference in outcome based on epigenetic subtype [26]. Similarly, in the EU-RHAB cohort, there is no significant difference in OS when TYR vs SHH vs MYC subgroups are compared [18]. Therefore, we conclude that there is no definitive evidence to date that any methylation group does better or worse. With larger cohorts, a trend for differential outcomes by subgroup may become more apparent.

Effect of radiation therapy

The timing, dose and field of radiation prescribed by each regimen vary. The DFCI protocol included focal XRT for patients with M0 disease and for children with M+ disease < 3yrs, while those ≥3 yrs of age with M+ disease received CSI. ACNS0333 recommended CSI for children with metastatic disease while children with localized disease received focal XRT. Of note, there were 3 children treated on ACNS0333 who were <3yrs of age with metastatic disease and received focal XRT only – all 3 were alive at last study follow-up suggesting that focal XRT may be sufficient for patients with M+ disease [32]. For children ≥3yrs of age without metastatic or residual disease, SJMB03 employs 23.4Gy CSI with a boost to the primary site.

The treatment-related toxicity associated with these regimens is significant, making it unlikely that further intensification of conventional therapy will lead to additional survival improvement for patients [16,17,19-21]. Additionally, given the devastating effects of radiation therapy in this very young patient population, strategies to avoid radiation should be developed whenever possible. As previously mentioned, patients treated on Head Start with no radiation therapy had a dismal prognosis, however most of the patients progressed early during

chemotherapy. A multi-institutional investigation of patients treated on or as per ACNS0333 found that in a cohort of 80 patients, children who received radiation therapy had a higher EFS and OS than children who did not experience disease progression on therapy and did not receive radiation therapy due to parent or physician preference [33]. When using the ACNS0333 regimen, induction and consolidation chemotherapy alone are not sufficient. While these studies demonstrate that AT/RT can be cured with aggressive, multimodal therapy, the relatively poor outcomes and therapy- associated toxicity highlight the need for novel treatment modalities to improve outcomes for children with AT/RT.

Summary of upfront AT/RT clinical trials

Although the aforementioned trials have shown improvement in outcomes for patients with AT/RT, they used varied approaches. Therefore, there is no established standard of care for newly diagnosed patients with AT/RT. Patients treated on ACNS0333 and the DFCI protocol had similar characteristics and outcomes. For children <3yrs of age, we recommend treatment as per ACNS0333 or the DFCI protocol. SJMB03 should also be considered for patients ≥3yrs of age with no residual or metastatic disease. Decisions regarding therapy must consider the age of the patient, size and location of the tumor, resources of the treating facility, and family preferences.

Completed trials for patients with relapsed/recurrent AT/RT

There have been only a few studies designed specifically for patients with recurrent AT/RT, although patients with relapsed/refractory AT/RT have been included in a variety of other early phase clinical trials.

The Pediatric Brain Tumor Consortium (PBTC) conducted an open-label phase II studies of oxaliplatin that included a stratum for recurrent AT/RT, along with medulloblastoma and supratentorial primitive neuroectodermal tumor (PNET) [34]. Of the 43 patients included on the trial, 5 had AT/RT. No AT/RT patients responded. However, one patient with AT/RT had prolonged stable disease for 17 courses while on study and received an additional 17 courses of oxaliplatin off protocol.

Based on a preclinical data suggesting activity of the cyclin-dependent kinase (CDK) 4/6 inhibitor ribociclib in malignant rhabdoid tumors (MRTs), a multi-center phase I study was pursued with this agent [35]. The study included an initial dose-escalation phase, followed by an expansion phase in patients with neuroblastoma and rhabdoid tumors, including AT/RT. Of the 32 patients enrolled on trial, 13 had AT/RT. Ribociclib was given once daily on a 3-weeks-on/1-week-off schedule in 28-day cycles. Although no responses were seen, 2 patients with AT/RT were found to have prolonged stable disease, remaining on treatment for 20 and 24 months.

Another targeted agent of interest in the relapse setting has been the Aurora A kinase inhibitor, alisertib. In a phase II study conducted by the COG in recurrent or refractory solid tumors and leukemia, 2 patients with AT/RT were included and treated. Although the drug was tolerable, no responses were seen in the AT/RT patients on trial. The objective response rate for all patients on trial (n=137) was less than 5% [36]. St. Jude Children's Research Hospital also conducted a phase II trial of single-agent alisertib specifically for recurrent or progressive AT/RT [37]. Thirty patients, representing all three molecular subgroups, were included. Only eight of 29 evaluable patients were without progressive disease by 12 weeks and thus the study did not meet the efficacy endpoint. However, PFS was 31%±8.2% at 6 months and 15.8%±6.5% at 1 year. One-third of patients had stable disease for greater than 6 months and two patients remained on therapy for greater than one year.

SMARCB1 or SMARCA4 deletions in AT/RT lead to an abnormal epigenetic landscape that transforms tumors and drives their rapid growth and survival. Therefore, targeting the abnormal epigenetics of these tumors is highly attractive. The deletion of SMARCB1 or SMARCA4 in AT/RT releases SWI/SNF inhibition of EZH2 methyltransferase activity leading to increased H3K27me3 repressive marks at the promoter regions of tumor suppressor and neuronal differentiating genes [38]. Knockdown of EZH2 in rhabdoid tumors prevents orthotopic tumor formation, demonstrating its importance in the establishment and growth of SMARCB1-deficient tumors [39]. The EZH2 inhibitor tazemetostat was studied in a phase 1 pediatric trial. Tazemetostat demonstrated one complete response and 5/21 objective responses in patients with AT/RT, with a median duration of 6.5 months [40,41]. In the COG-NCI Pediatric MATCH trial, tazemetostat demonstrated no objective responses in patients with AT/RT, however, 2/8 patients had stable disease at 6 and 13 months [42].

The current landscape of clinical trials for children with AT/RT

Currently, there is one ongoing clinic trial for newly diagnosed AT/RT patients at St Jude Children's Research Hospital, evaluating the Aurora A kinase inhibitor, alisertib, in combination with age-and risk-adaptive chemotherapy along with radiation therapy (NCT02114229). There are also ongoing early phase clinical trials for children with progressive or recurrent AT/RT investigating molecularly targeted agents as well as immunotherapies (Table 2). These studies are ongoing, and preliminary data are not yet available.

The Pacific Pediatric Neuro-oncology Consortium (PNOC) is conducting a phase I study of modified measles virus (MV-NIS) directly into the tumor bed for locally recurrent disease or into the subarachnoid space via lumbar puncture for those with disseminate recurrence (NCT02962167). This trial is based on preclinical data showing survival benefit in *in vivo* models of both focal and disseminated AT/RT when treated with measles virus injected either intratumorally or intraventricularly [43].

A multi-institutional trial based at Dana-Farber Cancer Institute is investigating the safety and efficacy of checkpoint inhibitor therapy (nivolumab in combination with ipilimumab) for children with relapsed/recurrent INI1-negative tumors (NCT04416568). Although tumor mutational burden is low in AT/RT, preclinical data supports the potential immunogenicity of AT/RT and use of immunotherapy in treatment [44].

The recent identification of B7-H3/CD276 as being highly expressed in pediatric brain tumors (including 100% of human AT/RT tumors with moderate to high level expression), in contrast to this antigen being expressed at low levels elsewhere in the body, suggests B7-H3 as a potential immunotherapeutic target [45]. Previous studies in human B7-H3-expressing colon, breast, and ovarian cancer cell lines showed that B7-H3 antibody-drug conjugates (ADC) killed B7-H3 expressing tumor cells as well as B7-H3 expressing tumor vasculature and spared normal cells, significantly extending the life of mice bearing flank or orthotopic tumors [46]. Similarly, the ADC m276-SL-PBD demonstrated broad activity against pediatric solid malignancies, including flank tumors of AT/RT [47]. B7-H3 generated CAR-T cell therapy when injected intratumorally or intraventricularly eradicated BT16 AT/RT orthotopic xenografts and persisted in the brain, preventing growth of tumors on rechallenge [48]. B7-H3 CAR-T cell clinical trials for children with relapsed/refractory solid tumors are open at several sites (NCT04897321, NCT04185038).

Potential novel agents for use in AT/RT

While *in vitro* high-throughput or hypothesis-based screening can provide an indication of activity of an agent against AT/RT, validating agents in pre-clinical models in general provides the best predictor of success in humans [49]. Embryonal cancer cells change their metabolism and epigenetics when grown as orthotopic tumors in mice compared to cells in culture and even flank tumors, making pre-clinical study in orthotopic models essential to justify the risks of testing novel agents within a clinical trial setting, especially for young children [50]. A number of promising clinical agents have advanced from the in vitro

Table 2
Ongoing Clinical Trials for Relapsed/Refractory AT/RT

Phase	Title	Therapeutic Category	AT/RT or INI-1 deficient tumor specific	Status
II	Phase 2 Proof of Concept Study of Nivolumab and Ipilimumab in Children and Young Adults With Relapsed or Refractory INI1-negative Cancers (NCT04416568)	Immunotherapy	Yes	Recruiting
I/II	TAZNI: A Phase I/II Combination Trial of Tazemetostat With Nivolumab and Ipilimumab for Children With INI-1 Negative or SMARCA4-Deficient Tumors (NCT05407441)	Immunotherapy + targeted agent	Yes	Not yet recruiting
II	A Phase 2 Study of Tiragolumab (NSC# 827799) and Atezolizumab (NSC# 783608) in Patients With Relapsed or Refractory SMARCB1 or SMARCA4 Deficient Tumors (NCT05286801)	Immunotherapy	Yes	Not yet recruiting
I	Combination Intraventricular Chemotherapy Pilot Study: Methotrexate and Etoposide Infusions Into the Fourth Ventricle or Resection Cavity in Children With Recurrent Posterior Fossa Brain Tumors (NCT02905110)	IT chemotherapy	No	Recruiting
I	A Phase 1 Study of Modified Measles Virus (MV-NIS) for the Treatment of Children and Young Adults With Recurrent Medulloblastoma or Recurrent Atypical Teratoid Rhabdoid Tumors (NCT02962167)	immunotherapy	No	Recruiting
I	Phase I Study to Evaluate the Safety and Tolerability of the CD40 Agonistic Monoclonal Antibody APX005M in Pediatric Subjects With Recurrent/Refractory Brain Tumors and Newly Diagnosed Brain Stem Glioma (NCT03389802)	Immunotherapy	No	Recruiting
I	Phase 1 Study of HER2-Specific CAR T Cell Locoregional Immunotherapy for HER2 Positive Recurrent/Refractory Pediatric Central Nervous System Tumors (NCT03500991)	Immunotherapy	No	Recruiting
I	Phase 1 Study of EGFR806-specific CAR T Cell Locoregional Immunotherapy for EGFR-positive Recurrent or Refractory Pediatric Central Nervous System Tumors (NCT03638167)	Immunotherapy	No	Recruiting
I	Phase 1 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 (NCT04185038)	Immunotherapy	No	Recruiting
I	Phase Ib Study of Oncolytic Polio/Rhinovirus Recombinant Against Recurrent Malignant Glioma in Children (NCT03043391)	Immunotherapy	No	Active, not recruiting
I	Phase 1 Trial of Engineered HSV G207 in Children With Recurrent or Refractory Cerebellar Brain Tumors (NCT03911388)	Immunotherapy	No	Recruiting
II	A Phase II Study of Metronomic and Targeted Anti-angiogenesis Therapy for Children With Recurrent/Progressive Medulloblastoma, Ependymoma and ATRT (NCT01356290)	Metronomic chemotherapy	No	Recruiting
II	AflacST1502: A Phase II Study of Sirolimus in Combination With Metronomic Chemotherapy in Children With Recurrent and/or Refractory Solid and CNS Tumors (NCT02574728)	Metronomic chemotherapy	No	Recruiting
I	Molecularly-Driven Doublet Therapy for All Children With Refractory or Recurrent CNS Malignant Neoplasms and Young Adults With Refractory or Recurrent SHH Medulloblastoma (NCT03434262)	Targeted agents	No	Recruiting
I	Phase 1 Study of 9-ING-41, a Glycogen Synthase Kinase 3 Beta (GSK 3β) Inhibitor, as a Single Agent or With Irinotecan, Irinotecan Plus Temozolomide, or With Cyclophosphamide Plus Topotecan in Pediatric Patients With Refractory Malignancies (NCT04239092)	Targeted agent + chemotherapy	No	Recruiting
I	Abemaciclib in Children With Newly Diagnosed Diffuse Intrinsic Pontine Glioma, and in Children With Recurrent and Refractory Solid Tumors Including Malignant Brain Tumors (NCT02644460)	Targeted agent	No	Recruiting
I	An Open-Label, Dose Escalation, Efficacy, and Safety Study of CLR 131 in Children, Adolescents, and Young Adults With Select Solid Tumors, Lymphoma, and Malignant Brain Tumors (NCT03478462)	Radioisotope	No	Recruiting

setting to demonstrating a survival advantage in pre-clinical in vivo models. Fig. 1 shows a summary cartoon of the mechanism of action of potential novel agents for treating AT/RT. Table 3 summarizes the clinical development of these potential novel agents.

Agents targeting mTOR

Several groups have demonstrated a vulnerability of AT/RT to mTOR inhibition, specifically using the TORC1/2 kinase inhibitor sapanisertib (also known as TAK228, MLN0128 and INK128) [51–53]. TAK228 increased survival as a single agent in mice bearing BT12 or CHLA06 orthotopic xenografts, but more impressively suppressed glutathione, and when combined with cisplatin, led to near doubling of median survival [51]. TAK228 and cisplatin combination treatment led to the long-term survival of nearly 40% of the treated mice.

One of the key targets of dual TORC1/2 inhibition is downregulation of the NRF2 transcription factor, which regulates the expression of genes involved in the response to cellular stress, redox homeostasis, metabolism, DNA repair, proliferation, and survival [54]. Inhibition of TORC1/2 and subsequent down-regulation of NRF2 disrupts AT/RT defenses against oxidative stress and cell death. Obatoclax is a brain-penetrant pan-BH3 inhibitor, which induces high levels of oxidative stress and apoptosis in AT/RT. TAK228 combined with obatoclax to increase median survival in mice bearing BT37 and CHLA06 orthotopic xenografts [54].

While the clinical development of sapanisertib is currently uncertain, these results led to the advancement of the highly brain penetrant PI3K/mTOR inhibitor paxalisib as a potential agent of interest. Paxalisib as a single agent led to an increase in survival of 20-30% in mice bearing orthotopic xenografts of CHLA-06 and BT12 [55]. Studies are

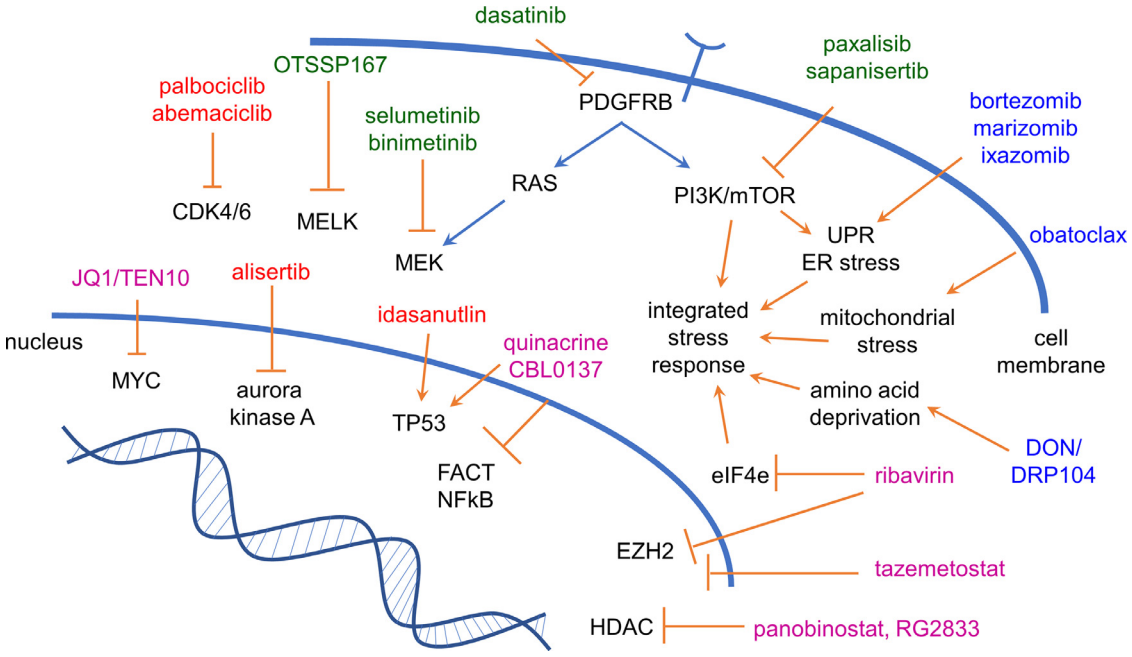

Fig. 1. Cartoon summarizing potential novel therapeutic agents for use in AT/RT. Potential agents are color coded, with signal transduction inhibitors in green, stress activators in blue, epigenetic agents in purple, and cell cycle acting agents indicated in red. Some agents act in multiple ways to inhibit AT/RT proliferation and promote death. Epigenetic alterations downstream of loss of SMARCB1 help AT/RT tumors to access developmentally significant growth and resistance programs that allow tumor cells to tolerate replicative, epigenetic and endoplasmic reticulum (ER) stress. Upregulation of platelet derived growth factor receptor B (PDGFB) may drive cell proliferation, and this may be blocked by the multi-kinase inhibitor dasatinib. Other agents targeting downstream effectors such as PI3K/mTOR, MEK and MELK may deprive AT/RT cells of key growth and survival pathways. Metabolic targeting agents such as 6-diazo-5-oxo-l-norleucine (DON) and its prodrug DRP-104 disrupt the metabolic dependencies of fast-growing AT/RT cells and synergize with traditional chemotherapy. Blocking the proteasome with inhibitors such as ixazomib may lead to further activation of the unfolded protein response (UPR) and ER stress. In combination with nutrient deprivation and induction of mitochondrial stress, these multiple stressors may lead to persistent activation of the integrated stress response and cell death. Epigenetic altering drugs such as histone deaceylase (HDAC) inhibitors panobinostat and RG2833 as well as enhancer of zest homologue 2 (EZH2) inhibitors such as tazemetostat and ribavirin may restore epigenetic balance to AT/RT. Similarly, JQ1 and other bromodomain inhibitors may block MYC activation, leading to decreased cell growth. The aurora kinase A inhibitor alisertib may block the mitotic activity of fast-growing AT/RT cells. Acting at the G1 cell cycle checkpoint, cyclin dependent kinase inhibitors such as palbociclib or abemaciclib also prevent AT/RT proliferation. DNA binding agents such as quinacrine and the curaxin CBL-0137 block transcription downstream of nuclear factor kappa B (NFkB) and separately lead to the accumulation and activation of the tumor suppressor TP53. Idasanutlin releases TP53 from MDM2 inhibition, allowing wild type TP53 to become active.

Table 3
Summary of novel agents under consideration for treatment of AT/RT

Agent	Target	Mouse in vivo data?	Adult RP2D?	Pediatric RP2D?
Signal transduction pathway inhibitors				
Paxalisib	PI3K/mTOR	Yes	Yes	Yes
Sapanisertib/TAK228	TORC1/2	Yes	Yes	No
Selumetinib	MEK	No	Yes	Yes
Binimetinib	MEK	Yes	Yes	Yes
OTSSP167	MELK	Yes	Yes	No
Dasatinib	PDGFR	Yes	Yes	Yes
Epigenetic modifiers				
Tazemetostat	EZH2	Yes	Yes	Yes
Panobinostat	Pan HDAC	Yes	Yes	Yes
RG2833	HDAC 1,3	No	No	No
Quinacrine/CBL0137	FACT	Yes	Yes	Yes
JQ1/TEN-10	BRD4/MYC	Yes	Yes	No
Cellular stress activators				
Ribavirin	eIF4e	Yes	Yes	Yes
DON/DRP104	Glutamine	Yes	Yes	Yes
Bortezomib/Marizomib/Ixazomib	Proteasome	Yes	Yes	Yes
Obatoclax	BCL-2, BCL-XL	Yes	Yes	No
Cell cycle targeting				
Alisertib	Aurora Kinase A	Yes	Yes	Yes
Palbociclib/Abemaciclib	CDK4/6	Yes	Yes	Yes
Idasanutlin	TP53	Yes	Yes	Yes
Immunotherapies				
Nivolumab/Ipilimumab	PD-1/CTLA-4	Yes	Yes	Yes
B7-H3 CAR-T cells	B7-H3	Yes	Yes	In progress
m276-SL-PBD	B7-H3	Yes	No	No
MV-NIS	CD46	Yes	Yes	In progress

currently ongoing, evaluating paxalisib's efficacy in combination with targeted as well as traditional chemotherapy. The PNOC AT/RT clinical trial working group is therefore considering advancing paxalisib as a combination therapy in the PNOC AT/RT adaptive clinical trial.

RTK inhibitors

An unbiased ATAC-seq-based approach led to the identification of an open region of chromatin in group 2A (corresponding to MYC subgroup of AT/RT tumors) near the *PDGFRB* gene promoter [29]. These tumors had increased expression of PDGFRB and sensitivity to the multi-kinase inhibitors nilotinib and dasatinib. Orthotopic xenografts of BT12 treated with dasatinib had modest but significantly longer survival compared to controls [29]. This data aligns with prior studies showing that some AT/RT cell lines demonstrate *in vitro* sensitivity to dasatinib [56].

MEK inhibitors

AT/RT primary tumors have increased expression of maternal embryonic leucine zipper kinase (MELK) as well as MAP kinase [57,58]. As monotherapy, the MEK inhibitors selumetinib and binimetinib inhibited the growth of AT/RT cells and induced apoptosis [58,59]. Binimetinib suppressed the growth of AT/RT flank xenograft but did not have efficacy against orthotopic xenografts [59]. Neither the MEK inhibitor trametinib nor the MELK inhibitor OTSSP167 significantly increased the survival of mice bearing AT/RT orthotopic xenografts, however combination therapy increased median survival from 22 to 32 days [57].

Metabolic targeting in AT/RT

Rapid proliferation in AT/RT drives dependencies on distinct metabolic pathways to support greater energetic needs and protect against toxic by-products of metabolism as compared to normal brain. Comprehensive metabolic profiling showed that AT/RT cells expressing high levels of MYC protein were dependent on glutamine signaling and were sensitive to glutamine metabolic inhibitors such as 6-diazo-5-oxo-L-norleucine (DON) [31]. DON as a single agent nearly doubled survival in mice bearing BT12 orthotopic xenografts. DON depleted glutathione and combined synergistically with carboplatin in mice bearing orthotopic xenografts of BT12 and CHLA06 [31]. Although DON is not currently available for clinical use, DON prodrugs are currently in clinical trials for adults with solid tumors [60–62] (NCT04471415).

Proteasome inhibitors

The high growth rate of rhabdoid tumors suggested that these cells might exhibit increased cellular stress. Mouse-derived malignant rhabdoid tumors have increased expression of unfolded protein response (UPR) and endoplasmic reticulum (ER) stress [63]. Treatment of these tumors with proteasome inhibitors such as bortezemib or ixazomib led to regression of tumors and extension of mouse survival [63]. Analysis of AT/RT showed an increase in proteasomal genes compared to normal brain. Targeting AT/RT with the proteasome inhibitor bortezomib killed tumor cells in vitro and extended the survival of mice bearing AT/RT orthotopic xenografts [64].

An unbiased drug screen of AT/RT identified proteasome inhibitors as being highly effective in vitro. The brain-penetrant proteasome inhibitor marizomib demonstrated activity against BT16 and MAF-737A AT/RT orthotopic xenografts [65]. Clinical development of marizomib is currently halted, however, the orally bioavailable and brain-penetrant proteasome inhibitor ixazomib also demonstrated activity against malignant rhabdoid tumor (MRT) in vitro and in vivo and killed AT/RT cells [63]. Ixazomib is currently in pediatric clinical trials in conjunction with anthracyclines for recurrent pre-B ALL (NCT03817320). Ixazomib was also noted in an unbiased drug screen of AT/RT primary cell lines, suppressing growth significantly across the board (J. Cain, personal communication). The positive preclinical results for ixazomib and other proteasome inhibitors suggest that this class may have activity against AT/RT in human patients and may warrant further exploration in a clinical trial.

CDK4/6 inhibitors

Cyclin-dependent kinase 4/6 (CDK 4/6) inhibitors such as ribociclib, palbociclib, and abemaciclib disrupt the proliferation of aggressive tumors with intact *RB* signaling. CDK 4/6 inhibitors prevent the growth of embryonal tumors *in vitro* and in orthotopic xenografts [49,66]. In AT/RT, palbociclib alone increased median survival of mice bearing orthotopic BT12 xenografts by 60 percent [67]. Combining palbociclib with radiation therapy led to a more than doubling of median survival compared to control in BT16 orthotopic xenografts [67]. Mark et al., using a CRISPR-genome-wide screen, identified CDK4/6 as a dependency in AT/RT and showed that single-agent abemeciclib significantly extended the life of mice bearing orthotopic BT16 AT/RT xenografts [68]. While single agent ribociclib did not show response in AT/RT patients in a phase I study [35], a phase 1A/1B clinical trial of abemaciclib in combination with temozolomide and irinotecan is currently enrolling pediatric patients with brain and other solid tumors (NCT04238819).

Epigenetic therapies

The anti-viral drug ribavirin has structural similarity to the EZH2 inhibitor 3-deazaneplanocin A (DZNep) [69] and efficiently downregulates EZH2 in AT/RT cells [70]. Ribavirin kills AT/RT tumor cells in part by blocking eIF4E and inducing apoptosis. Ribavirin penetrates the brain, and ribavirin treatment of mice bearing BT12 orthotopic xenografts led to an increase in median survival of 56 compared to 37 days for vehicle-treated mice [70].

Despite increases in EZH2 methyltransferase activity in AT/RT, there are important regions of the genome activated by H3K27 acetylation [38]. The bromodomain and extraterminal (BET) domain family of proteins are required for this H3K27 acetylation. JQ1 is a highly specific inhibitor of BET and BET bromodomain-containing protein 4 (BRD4) [14]. JQ1 is especially effective at targeting MYC driven AT/RT, extending survival in a MYC-driven BT12 orthotopic xenograft [71]. JQ1 and the EZH2 inhibitor GSK126 combined to extend median survival by more than 50% of mice bearing BT12 orthotopic xenografts [72]. These drugs in combination also significantly extended survival in a BT16 orthotopic xenograft model of AT/RT [72]. TEN-010/RO6870810 is a JQ1 analog that was explored in several clinical trials in adult patients (NCT01987362, NCT03068351).

The histone deaceytlase inhibitor (HDAC) panobinostat suppressed the growth of AT/RT cell lines at nanomolar concentrations and induced the differentiation of these cell lines along a neuronal lineage [73]. Combinations of HDAC and mTOR inhibitors drive embryonal cell differentiation in rhabdoid tumors [74]. Treatment of mice bearing BT12 orthotopic xenografts with daily low dose panobinostat for 28 days led to decreased tumor growth as measured by bioluminescent imaging and statistically significant extension of overall survival [73]. Interestingly, when panobinostat treatment stopped after 28 days, the tumors rapidly progressed, underscoring the epigenetic plasticity inherent in AT/RT and other epigenetically driven tumors. These results were concordant with those observed in a prior study in which panobinostat treatment of malignant rhabdoid tumors led to suppression of tumor growth and differentiation along an osteoblastic program [75]. A clinical trial of panobinostat as maintenance therapy in AT/RT recently closed due to drug supply issues (NCT04897880).

The HDAC 1,3, brain-penetrant inhibitor RG2833 also suppressed AT/RT tumor cell growth, promoted apoptosis and upregulated tumor suppressor expression [55]. This inhibitor was originally designed to penetrate the brain for treatment of neuro-degenerative diseases and

was well tolerated in humans in early clinical trials [76,77]. RG2833 induced histone de-acetylation in AT/RT orthotopic xenografts and may synergize with other targeted or traditional chemotherapy in AT/RT [58].

Curaxin (CBL0137) is a DNA minor groove binding drug that is related to the anti-malarial drug quinacrine [78]. Curaxin disrupts the FAcilitates Chromatin Transcriiption (FACT) complex and as monotherapy extends the life of mice bearing medulloblastoma orthotopic xenografts [79]. Curaxin also has activity against AT/RT cells *in vitro* and suppresses the growth of MRT flank xenografts [80]. Quinacrine itself kills AT/RT cells, and in conjunction with the ATP-Binding Cassette transporter inhibitor Elacridar extends the life of mice with bearing BT37 orthotopic xenografts [81]. CBL0137 has improved brain penetration and is less likely to be a substrate for multi-drug resistance (MDR) proteins, making it an improvement on quinacrine [78]. A phase I/II clinical trial of CBL0137 in pediatric patients with solid tumors, including brain tumors, is currently ongoing (NCT04870944).

Other cell cycle inhibitors

In addition to the previously mentioned Aurora Kinase A inhibitor alisertib, drugs that activate p53 are also active in AT/RT preclinical models. Mutations in TP53 are rare in AT/RT, but the TP53 binding protein MDM2 is highly expressed [82]. Treatment with the MDM2 inhibitor idasnutlin killed AT/RT tumor cells and extended survival of mice bearing orthotopic MAF737 xenografts [82]. The DNA-binding drug quinacrine also induces expression of activated p53 in AT/RT, suggesting that activation of p53 may contribute, along with disruption of FACT, to the activity of quinacrine and Curaxin/CBL-0137 [81].

Immunotherapies

AT/RT has the lowest mutational burden in coding genes of any aggressive human malignancy, and other mutations are rare and inconsistent [29], suggesting that there is a lack of suitable neoantigens for immune attack. However, immune profiling of AT/RT primary tumors has shown that they are richly infiltrated with macrophages, CD8+, CD4+ T-cell and NK cells [44]. Tumor resident and exhausted memory T-cells were increased in AT/RT tumors. Perhaps due to their epigenetic dysregulation, human AT/RT tumors express increased levels of endogenous retroviral RNA, leading to increased interferon-regulated gene expression [44]. Treatment of a syngeneic mouse model of MYC-driven AT/RT growing in flanks with PD-1 immune checkpoint inhibitor led to delayed tumor growth and increased tumor rejection on rechallenge [44].

Landscape of upcoming clinical trials for children with AT/RT

Due to the rarity of this disease and still unacceptably high rate of recurrence and death, novel clinical trial designs are needed to investigate novel agents more efficiently and to provide new treatment options to as many children with AT/RT as possible. PNOC is developing a multi-arm clinical trial for patients with relapsed/recurrent/refractory AT/RT where novel agents will be incorporated into the study schema as preclinical data emerge about their efficacy against AT/RT. The trial will have multiple treatment arms based on the agents under investigation with some arms enrolling patients to determine safety/tolerability and recommended dosing, while other arms will interrogate the efficacy of agents with pre-established pediatric dosing. Some arms will be investigating single agents while others will be designed as combination studies. Patients enrolled on the trial will be able to be treated sequentially on different arms of the study based on their response to the different agents. This will allow patients to be treated with a number of different agents/combinations of agents without having to experience prolonged delays between therapies. This type of design also allows investigators to quickly move novel therapies into the clinic without undo delays associated with the development of a new clinical trial. In parallel, PNOC is also creating a comprehensive registry of patients with AT/RT inclusive of complete clinical, radiographic, and molecular data. These data will be used to create an external control cohort that will serve as the comparator cohort for determination of the trial's outcome measures.

Conclusion

While current available therapies utilizing intensive multimodal therapies have led to improvement in outcomes for patients with AT/RT, the risk of recurrence and death remains at about 50%, and survivors carry a high burden of treatment related toxicity, including neurocognitive impairment [83]. As such, continued efforts to improve treatment options for patients with AT/RT in the upfront and relapsed setting is imperative. Bringing novel therapies into prospective clinical trials for AT/RT is needed as part of the efforts to improve outcomes and decrease toxicity. There are numerous novel therapeutics with biologic rationale and supportive pre-clinical data that are either currently being evaluated or soon to be incorporated into clinical trials for AT/RT. As we learn more about the molecular and epigenetic drivers of AT/RT, more data will likely emerge in the future. Given the rarity of AT/RT, as well as the emerging understanding of the molecular heterogeneity of the subgroups and their correlation to response and outcomes, the use of innovative clinical trial designs and international collaborations will be paramount in making further progress in the treatment of AT/RT.

Author contributions

Elizabeth Alva: – writing – original draft, editing, data curation. **Jeffrey Rubens:** writing – original draft, review and editing, data curation. **Susan Chi:** review and editing, data curation. **Tom Rosenberg:** review and editing, data curation. **Alyssa Reddy:** review and editing, data curation. **Eric Raabe:** writing – original draft, review and editing, conceptualization, data curation. **Ashley Margol:** writing – original draft, review and editing, editing, conceptualization, data curation.

Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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