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REVIEW

Current Molecular and Clinical Landscape of ATRT – The Link to Future Therapies

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Abstract: ATRT is a highly aggressive and rare pediatric CNS tumor of very young children. Its genetic hallmark is bi-allelic inactivation of *SMARCB1* encoding INI1. Rarely *SMARCA4* encoding BRG1 is affected. Up to 30% are associated with constitutional heterozygous pathogenic variants in one of the two genes, giving rise to the Rhabdoid-Tumor-Predisposition-Syndromes (RTPS) 1 and 2. Characteristic DNA methylation profiles distinguish ATRT from other *SMARCB1*-deficient entities. Three distinct subtypes ATRT-MYC, -TYR, and -SHH are on record. ATRT-SHH may be further divided into the subgroups ATRT-SHH1A, -SHH1B, and -SHH2. The cure of ATRT remains challenging, notwithstanding an increasing understanding of molecular pathomechanisms and genetic background. The implementation of multimodal institutional treatment protocols has improved prognosis. Regardless of treatment approaches, clinical risk factors such as age, metastases, and DNA methylation subtype affect survival probability. We provide a critical appraisal of current conventional multimodal regimens and emerging targeted treatment approaches investigated in clinical trials and entity-specific registries. Intense treatment approaches featuring radiotherapy (RT) and high-dose chemotherapy (HDCT) face the difficulty of balancing tumor control and treatment-related toxicity. Current approaches focus on minimizing radiation fields by proton beam therapy or to withhold RT in HDCT-only approaches. Still, a 40–75% relapse rate upon first-line treatment reveals the need for novel treatment strategies in primary and even more in recurrent/refractory (r/r) disease. Among targeted treatments, immune checkpoint inhibitors and epigenetically active agents appear most promising. Success remains limited in single agent approaches. We hypothesize that mechanism-informed combination therapy will enhance response, as the low mutational burden of ATRT may contribute to acquiring resistance to single targeted agents. As DNA methylation group-specific gene expression profiles appear to influence response to distinct agents, the future treatment of ATRT should respect clinical and biological heterogeneity in risk group adjusted treatment protocols.

Keywords: SWI/SNF related matrix associated, actin dependent regulator of chromatin, subfamily b, member 1, SMARCB1, atypical teratoid rhabdoid tumor, ATRT, central nervous system, CNS, treatment, pediatric, cell cycle

The Burden of Atypical Teratoid Rhabdoid Tumors

ATRT – A Rare and Unique Entity

Atypical Teratoid Rhabdoid Tumors (ATRTs) are WHO grade 4 embryonal CNS tumors.[1] They predominantly affect children and young adults with incidences ranging from 0.3/100,000 to 0.6/100,000 in the first year of life and 0.03/100,000 to 0.26/100,000 for children between 5 and 9 years of age in the USA and Europe, respectively.[2,3]

Typically, ATRTs are located infratentorial (60%) and in 22% are located in the cerebral hemispheres, with the mesencephalon and the pineal region being less common locations (each 4%). Primary intraspinal ATRTs are a rarity (1–2%)[4,5] and occasionally cannot be distinguished clearly from spinal extracranial, extrarenal malignant Rhabdoid Tumors (eMRT).[6] Rhabdoid tumors tend to appear synchronously: In 6% of all cases, two or more rhabdoid tumors are detected

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at different anatomic sites, with the CNS being one in most instances.[4,7–11] Dissemination and metastases along the cerebrospinal fluid (CSF) compartment are common and initially diagnosed in 20−30% of cases.[4,5,12]

Diagnosis of ATRT can be confirmed immunohistochemically by the nuclear loss of SMARCB1 (INI1)-staining. In comparison to other *SMARCB1*-deficient CNS tumors, ATRT is presented with specific DNA methylation profiles. Histopathologic differential diagnoses in the scope of *SMARCB1*-deficient tumor entities are listed in Table 1 and comprise LGDIT,[13] desmoplastic myxoid tumor, *SMARB1*-mutant,[14,15] CRINET,[16,17] PXA,[18] or *SMARCB1*-deficient malignant tumors in the context of Li-Fraumeni syndrome.[19]

ATRT Exhibit Uniform Inactivation of SMARCB1 or SMARCA4 but Comprise Distinct Molecular Subgroups

Presenting rather stable copy number variation profiles, rhabdoid tumors demonstrate pathogenic variants in only a few genes with *SMARCB1* or *SMARCA4* consistently inactivated in tumor cells. *SMARCB1 and SMARCA4* encode for subunits of the SWI/SNF chromatin remodeling complex. ATRT is, thus, a disease intimately linked to epigenetic deregulation.[27,28] ATRT can be grouped into three distinct major molecular subtypes, ATRT-MYC, -SHH and -TYR. Each of these is associated with distinct DNA-methylation and gene expression profiles as well as anatomic and clinical characteristics.[24,27] The level of immune cell infiltration and immune checkpoint expression also differ between ATRT subgroups.[29] ATRT-MYC tumors exhibit similarities with the DNA methylation subgroups of extracranial rhabdoid tumors (group 3 = RTK like and group 4 = extra-renal MRT like).[29] ATRT-SHH was found to cluster into further subgroups. Federico et al described three distinct subgroups with respect to DNA-methylation profile: ATRT-SHH1A, −1B, and SHH2. ATRT-SHH1B are located primarily supratentorial, affect older children (median age for -SHH1B 107 months, -SHH1A 18 months, -SHH2 13 months), and are associated with a significantly improved survival probability compared to -SHH1A and -SHH2.[30] By converging imaging and multi-omics analyses, Lobón-Iglesias et al detected two distinct ATRT-SHH subgroups: CAL SHH ATRT (cerebral anterior lobe, overexpression in *EN2*) and BG/IV SHH ATRT (basal ganglia, intra ventricular, overexpression in *OLIG2*), which may be correspond to ATRT-SHH2 and ATRT SHH-1A, respectively.[31] Taken together, this strongly suggests the existence of distinct ATRT-SHH subgroups.

The relevance of DNA methylation subtypes as prognostic markers and therapeutic targets in an extremely rare disease remains currently unresolved. We could show that features of the ATRT-TYR group in combination with older age at diagnosis bear a favorable prognostic significance (5-year OS 0% and 70% in ATRT-non-TYR and <1 year and ATRT-TYR and ≥1 year, respectively; n=143). Upadhyaya et al confirmed this beneficial impact of ATRT-TYR but detected a diminished effect among ATRTs in M0 (n=22).[32] For extracranial malignant rhabdoid tumors (eMRT), metastatic disease, GTR, and germ line mutation (GLM) distinguish high risk from standard risk groups.[33] Future research will need to focus on evaluating potential confounders. Nevertheless, the fifth edition of the WHO classification of Tumors of the Central Nervous System (CNS 5) sheds light on the descriptive importance of the three distinct methylation subtypes of ATRT.[1]

Rhabdoid-Tumor-Predisposition Syndrome

SWI/SNF deficiency in rhabdoid tumors is a result of biallelic loss of *SMARCB1* or *SMARCA4*. In approximately 25–30%[4,21–23] of the patients with ATRT the first hit is a constitutional event, ie, it is supposed to occur in the germline and leads to heterozygous inactivation of one allele of the respective gene in all cells of the body. Such constitutional inactivation (often also called germ line mutation, GLM) occurs de novo, as in most cases of constitutional inactivation of *SMARCB1*, or is inherited from a parent, as for most cases of *SMARCA4*. Constitutional inactivation of one copy of *SMARCB1* or *SMARCA4* gives rise to rhabdoid tumor predisposition syndrome (RTPS; RTPS1, GLM in *SMARCB1*; RTPS2, GLM in *SMARCA4*). Penetrance is considered high for RTPS1 but incomplete for RTPS2. Clinical features of RTPS include an earlier onset of disease and multiple synchronous tumor sites. Clustering of rhabdoid tumors and SWI/SNF deficient tumors in families has been reported, and frequently due to de novo mutation.[34–36] Despite an inferior prognostic outlook and severe clinical courses, a significant number of long-time survivors affected by RTPS are on record.[37–40]

Table 1 Differential Diagnoses of *SMARCB1* Deficient (Pediatric) CNS Tumors

Tumor Grade	Tumor Type	Histopathology	Localization	Genomic Alterations	DNA Methylation Profile	Age at Diagnosis	Prognosis
Low	LGDIT, SMARCB1 mutant[13]	Low to moderate cellularity, pleomorphic glial and neuronal cells, Ki67 8%	Supratentorial	Homozygous *SMARCB1*-deletion	Similarity to ATRT-MYC	Median 16 years	Good response to multimodal treatment, but potential to progress to ATRT
Low	Desmoplastic myxoid tumor, SMARCB1-mutant[15]	Spindle and epithelioid cells embedded in a desmoplastic stroma, loose myxoid matrix; Ki67 3%	Pineal region	Heterozygous or homozygous *SMARCB1* deletion	Distinct DNA methylation profile in proximity to ATRT-MYC	Median 40 years (15–61 years)	Stable disease without CT, RT following complete surgical resection
High	ATRT	Poorly differentiated, multi-lineage phenotype, glial, mesenchymal, epithelial components, rhabdoid cells, small round blue cells[5,20]	Supratentorial, infratentorial and (less common) spinal[4]	Biallelic alterations in *SMARCB1*/ *SMARCA4*, GLM in 30%[4,21–23]	ATRT • TYR • SHH • MYC[24]	Median 18 months[25]	5-year OS 0–71% dependent on risk factors[4]
High	Cribriform neuroepithelial tumor (CRINET)[16]	Cribriform growth pattern with neuroepithelial tumor cells; Ki67/MIB1 30%,	Often intraventricular	Large heterozygous deletions of 22q + *SMARCB1* mutations, often affecting the C-terminus[26]	Similarity with ATRT-TYR	10–26 months	Good response to multimodal treatment (1 partial resection, CT, RT; 1 GTR, CT)[16]
High	ATRT with molecular features of PXA[18]	Rhabdoid cells, brisk mitotic activity, geographic necroses, Ki67 high 15–60%	Supratentorial, temporal lobe	Homozygous *SMARCB1* deletion, genetic features of PXA (homozygous *CDKN2A/B deletion*), gain of whole chromosome 7 *BRAF* V600E mutations)	Similarity with PXA	10–18 years, (1 case report of a 62-year old female)	To be determined, BRAF mutation as novel therapeutic target?
High	*SMARCB1*-deficient malignant brain tumors in the context of Li-Fraumeni syndrome[19]	Glial phenotype, pleomorphic nuclei, fibrillary process, no nuclear accumulation of p53 protein, scattered rhabdoid tumor cells[4]	Supratentorial, temporal lobe	Complex copy number alterations and *TP53* mutation	Similarity with ATRT or malignant gliomas.	5–19 years	Depending on histopathological profile; to be determined

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Germline predisposition in *SMARCB1/SMARCA4*-deficient ATRT is associated with younger age at diagnosis, which is also a common feature of other well-known genetic tumor syndromes like BRCA-related cancer predisposition or retinoblastoma. Nevertheless, in contrast to other genetic tumor syndromes, younger age itself may explain inferior prognosis as the spectrum of age adjusted treatment approaches is extremely limited (ie, aggressive surgery or radiotherapy). Moreover, it might have to be taken into account that *SMARCB1* and *SMARCA4* are more or less ubiquitously expressed and play a major role in chromatin remodeling and epigenetic control in various cell compartments. As an example, expression levels of *SMARCB1* have been linked to the immunoglobulin V-region mutational load in germinal center B-cells[41] and somatic inactivation of SMARCA4 is common in germinal center B-cell derived lymphomas like Burkitt lymphoma.[42] It is, thus, intriguing to speculate, that haploinsufficiency, eg, in cell compartments other than tumor cells, like in cells of immunological compartments, might contribute to the aggressive biological behavior of ATRT in patients with constitutional SMARCB1 alterations, eg, via contributing to immune escape.

Clinical Management of Atypical Teratoid Rhabdoid Tumors – Current Conventional Therapeutic Approaches

Reflecting the rarity of ATRT, international guidelines for clinical practice remain limited. The "Canadian Pediatric Neuro-Oncology Standards of Practice", published in 2020, is one of the few detailed clinical practice guidelines publicly available.[43]

Lessons from Phase III Clinical Trials and Entity Specific Registries

The diversity of data sets and treatment approaches in small cohorts explain the complexity of meta-analyses on which to base recommendations for therapy. Treatment elements such as maximal safe resection, conventional or high-dose chemotherapy (CT vs HDCT), and radiotherapy (RT) represent the most important components of first-line treatment in clinical trials and consensus therapy recommendations (eg, EU-RHAB, ACNS0333, Medical University of Vienna, DFCI, Head Start, HIT-SKK92).[44–50] Controversy exists about the role of the extent of surgery, as some investigators describe a gross total resection (GTR) as a favorable prognostic factor,[4,12,45,51–55] while others cannot confirm any statistically significant influence[44,56–58] The potential role of neoadjuvant chemotherapy in unresectable tumors awaits evaluation. A further, thus far unresolved, question is the role of radiotherapy in consolidation, ie, whether it may be postponed using intrathecal chemotherapy or at best replaced by HDCT.

Table 2 provides an overview of the results of inconsistently treated larger cohorts of ATRT such as phase III trials and demonstrates advantages and disadvantages. As results of these have been published several years ago, trial design and results are not the emphasis of this review. Instead, our aim is to focus on lessons learned from conventional treatment and to outline open tasks for future treatment approaches.

Multimodal Treatment Approaches in the Management of ATRT

Implementation of institutional multimodal approaches has remarkably improved the prognosis of selected cohorts of ATRT in 2-y and 5-year overall survival to almost 70%.[4,56] It remains at 30–40% or less in unfavorable cohorts, including those with initial metastatic disease and age below 1 year.[4,45,57]

The role of radiotherapy has been the subject of much debate, as it has been shown to be effective,[12,51,58,60] while adverse effects on the physical and cognitive development, as well as severe complications such as radiation necrosis,[61–65] have raised the question of viable alternatives.

Current investigations suggest that radiotherapy in younger children (<3 years) may be beneficial for tumor control[66] but bears the risk of disastrous late effects at this vulnerable age.[67] Sequencing RT to the end of treatment may be a solution to allow for further maturation of the CNS and thus reducing harm.[65] Studies by Yamasaki et al and Yang et al indicate that early vs late RT does not affect the treatment success in children below 3 years.[58,66,68–71] Current evidence indicates that proton beam therapy (PBT) with doses equivalent to photons may achieve comparable results in terms of local tumor control and overall survival while potentially saving patients from toxicities, ie, symptomatic radiation necrosis. Still, a significant risk of distant treatment failures remains, ie, outside the former field of radiotherapy.[69,70,72,73]

Table 2 Overview of the Results of Clinical Phase III Trials and Consensus Regimens Exclusively in ATRT

Phase	Title and Identifier	PI	Completion Date	Treatment	Results Published	Comments	Reference	Topic
III	Children's Oncology Group Trial ACNS0333 (NCT00653068)	A. Reddy	August, 2023	Maximal safe tumor resection 2 cycles induction 3 cycles consolidation plus RT (sequence dependent on age and tumor localization) 4-year Follow up period	65 patients 4-year EFS 37% 4-year OS 43% < 36 months 4-year EFS 35% (improved compared to historical cohort) 3 toxic deaths ≥ 36 months 4-year EFS 48% 4-year OS 57% 1 toxic death 4-year OS 49% for "RT before consolidation" 4-year OS 48% for "consolidation before RT" 50% treatment failure (16/33 local failure)	Two treatment arms, but non-randomized Challenging cohort (83% younger than 36 months, 30% younger than 12 months, 37% with M+, 38% with GTR) Improved survival for patients younger than 36 months High amount of safety relevant toxicity No information on cognitive and psychological late effects	[45]	Radiotherapy and HDCT

(*Continued*)

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Table 2 (Continued).

Phase	Title and Identifier	PI	Completion Date	Treatment	Results Published	Comments	Reference	Topic
II	Multi-institutional Phase II clinical trial to test efficacy or aggressive multimodality approach for children with newly diagnosed ATRT (DFCI)	S N Chi	May, 2008	Maximal safe tumor resection Modified IRS-III including intrathecal chemotherapy: Pre-RT chemotherapy Chemoradiation post-RT induction Maintenance therapy Continuation therapy	20 patients 2-year PFS 53% (± 13%) 2-year OS 70% (± 10%) 5-year OS 49.6% 10-year OS 44.7% Median survival 5.2 years 58% objective response to induction therapy 38% response to RT 8 long-time survivors (median FU 14.7 years; median 1.9 years at diagnosis, localized disease, RT, 6/8 with upfront GTR/STR) Succumbed (10): 5/10 M+, 7/10 with upfront biopsy/ partial resection 40% refractory or recurrent disease (max 4 years of data reporting) 1 toxic death (pneumococcal sepsis)	Prospective multicenter trial, single arm, Beneficial cohort (Median age at diagnosis 26 months (60% younger than 36 months, 20% younger than 12 months), 30% with M+, 50% with GTR) Short follow up period Small cohort size	[56,59]	Radiotherapy, intrathecal chemotherapy

registry	The Canadian Paediatric Brain Tumor Consortium experience (CBTC)	L. Lafay-Cousin		Maximal safe tumor resection 10/50 in palliation 22/40 conventional chemotherapy (baby brain, IRS III like, ICE regimens, 9/22 anthracycline based) 18/40 HDCT (Head start, Triple Carboplatin/ Thiotepa, MTX induction + Triple Carboplatin/ Thiotepa) 9/40 intrathecal chemotherapy 21/40 radiation	50 patients Projected 2-year OS 36.4% ± 7.7 Median time of survival 13.5 months 75% with progress/relapse (median time to progression 5.5 months) Significant prognostic risk factors: **GTR**: 2-year OS (GTR) 60% ±12.6) 2-year OS (non GTR) 21.7% ± 8.5, p = 0.03 **HDCT**: 2-year OS (HDCT) 47.9% ±12.1 2-year OS (non HDCT) 27.3% ± 9.5, p= 0.036 Not-significant factors: **Age**: median survival time: 9.6 months in patients < 12 months 17.4 months in patients 12–36 months: 19.1 months in patients > 36 months: Upfront radiation no survival benefit! 6/12 survivors without radiation	Multicentric retrospective analysis Small cohort (n=50) Unfavorable cohort (median age at diagnosis 16.7 months, 76% younger than 36 months, 38% with M+, 30% with GTR, 2 synchronous MRT, 3 with diagnosed GLM) Best overall response not evaluated/not reported (radiographic CR, PR, SD etc) 75% refractory/ recurrent disease (max. 32 months) Multicenter Neuropsychological results in long-time survivors published three years later		

(*Continued*)

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Table 2 (Continued).

Phase	Title and Identifier	PI	Completion Date	Treatment	Results Published	Comments	Reference	Topic
Registry	EU-RHAB	M C. Frühwald	May, 2023	Maximal safe tumor resection Anthracycline based chemotherapy (9 to 12 courses) Age-dependent radiotherapy (no RT in < 18 months) HDCT (Carboplatin/ Thiotepa + ASCT) on physician's choice	143 patients 5-year OS 34.7 ± 4.5% 5-year EFS 30.5 ± 4.2% Median follow up 49.9 months 64% relapse or progression (mainly locally) 57% died due the time of analysis 3 cases of secondary malignancies (AML) No toxic death Independent significant prognostic factors: Age at diagnosis (< 1 year vs ≥ 1 year) DNA methylation subtype (TYR vs non-TYR) Dependent significant prognostic factors: Synchronous tumor (yes vs no) Metastases (M0 vs M+) Radiotherapy (yes vs no) Complete remission (yes vs. no) GLM (yes vs no)	Multicentric retrospective analysis Unfavorable cohort (median age at diagnosis 29.5 months, 86% younger than 36 months (35% younger than 12 months, 51% 12–35 months), 30% with M+, 34% with GTR) Large cohort Genetic and molecular information available	[4]	

Several international centers recommend the addition of intraventricular chemotherapy (IVCT) to conventional chemotherapy to avoid radiotherapy (EU-RHAB, DFCI-AT/RT, and MUV),[46,50,56,74,75] as IVCT in metastatic ATRT has significantly improved 2-year OS (65% vs 17.3%) as suggested by a meta-analysis.[50] The risk of severe encephalopathy, mainly leukoencephalopathy, due to accidental intraparenchymal methotrexate instillation[76,77] or diapedesis of MTX in ventricular obstruction[78] is a significant risk. There are no controlled or randomized phase III trials investigating the effect of IVCT in ATRT, thus evidence remains contentious. Currently recruiting clinical trials use the intrathecal route to administer experimental agents such as CAR-T cells, immunovirus, or immune-radiotherapy (see below).

Multimodal approaches including high-dose chemotherapy with autologous stem cell rescue (HDCT/ASCT) are associated with a significantly improved survival, especially in the first and second year from diagnosis.[79] HDCT may be considered an efficient treatment approach in children, who need bridging therapy until RT is feasible.[45] Reports from the Canadian Brain Tumor Consortium and the Head Start III trial describe encouraging success of radiotherapy-witholding HDCT in patients younger than 36 months (ie, prolonged survival even in patients with initial metastatic disease).[47,54] As infants are an extremely challenging cohort,[80] appropriate treatment regimens minimizing toxicity are urgently needed. The significant therapeutic successes of ACSN0333 and CCG99703 were unfortunately accompanied by substantial treatment-related toxicities and even toxic deaths (n=2 CNS necrosis) predominantly in patients below 36 months.[45]

The *Canadian Pediatric Neuro-Oncology Standards of Practice* features both CCG 99703 and ACNS0333 protocols as first-line therapy of ATRT, while radiotherapy instead serves as an additional option as a "physicians'-decision-only" approach. Recommendations reflect expert opinions and consensus statements rather than evidence-based data.[43] Data proving the superiority of HDCT approaches versus conventional chemotherapy and radiotherapy-based approaches, ie, derived from randomized controlled clinical trials are missing. In the largest cohort of consistently treated ATRT (n=143, EU-RHAB) HDCT did not significantly improve survival. Here, 5-year OS and 5-year EFS of 35% and 30% were achieved by multimodality treatment approaches based on physicians' choice, according to a European consensus strategy (based on DFCI and IRS III protocols). This consisted of surgery, anthracycline-based chemotherapy, and age-dependent administration of RT (no RT in children < 18 months) or HDCT instead. In total, 34 patients were treated with consolidation therapy in the form of HDCT/ASCT (carboplatin, thiotepa), only. However, multivariate analysis could not demonstrate any significant influence of RT-withholding approaches.[4]

As baseline conditions and survival in this cohort were comparable to those of the cohort within ACNS0333 (see Table 2), we suggest that the question whether HDCT featuring protocols (eg, ASCNS0333,[45] Canadian Brain Tumor Consortium[81]) are preferable over those including radiotherapy (eg, DFCI[56] and EU-RHAB[4]) deserves validation in a randomized setting in larger cohorts. The ongoing SIOPE ATRT01 trial (Eudra-CT 2018-003335-29) investigates the impact of isolated HDCT with autologous stem cell rescue as consolidation therapy.

Remaining High Risk for Relapse and Refractory Disease

Even though institutional multimodal treatment approaches have improved survival probability, a significant risk of recurrent or refractory disease remains. Progressive disease still occurs in 40–75%.[4,45,57] There is no international consensus on how to treat patients with r/r ATRT. This situation is the focus of Phase I and II clinical trials. Very limited data exist on real word experience such as individual experimental treatment approaches.

Therapeutic Approaches Supported by Genetic Analyses:MAPPYACT, eSMART, INFORM

To overcome limitations of conventional therapy, "one size does not fit all", targeted anti-cancer medicine studies incl. MAPPYACT, eSMART, MATCH, and INFORM attempt to identify genetic and molecular targets for individualized treatment approaches.

The evidence available from these approaches reveals two major problems: On the one hand, apart from *SMARCB1* no other repetitive cancer-specific genetic alterations have been detected (INFORM[82] and MAPPYACT[83]). Identification of suitable genetic biomarkers to deduce specific treatment targets thus remains challenging.

On the other hand, albeit potential drug targets incl. CDKs, aurora kinase A, immune checkpoint receptors, and ligands are highly expressed in selected ATRT, targeting these induced significant treatment responses in very few ATRTs

only.[83] Expression profiles alone are thus not sufficient to predict response to single agent targeted therapy. Deciphering pathomechanisms of resistance to the EZH2 inhibitor tazemetostat, Kazansky et al identified specific acquired mutations in resistant rhabdoid tumor cell lines that appear to be responsible for treatment failure. At the same time, these analyses demonstrated potential targets for synthetic lethality (in cell lines and xenograft mouse model).[84] We discuss the use of synthetic lethality in the setting of clinical trials below.

Remaining Challenges in r/r ATRT

Randomized phase III trials may help consolidate evidence for risk factors and treatment elements. Future research will have to target the role of conventional compounds such as repurposed cytostatics (incl. IVCT) but also radiotherapy modalities, as well as smart combination elements.[85] The concept of future clinical trials depends on international (drug) availability and the capacity to recruit suitable cohorts. The fortunately increasing number of long-time survivors highlights the need to attend to and study the physical and mental development as well as aspects of quality of life in survivors. Treatment approaches for the special cohort of infants necessitate the highest level of diligence in designing safe and efficient therapeutic trials.[80]

Potential Targeted Therapeutic Approaches to ATRT

Table 3 provides an overview of potential therapeutic targets investigated in ongoing clinical trials. These approaches target either cell cycle activating pathways and checkpoints, DNA-repair or histone modifications, the immune system–cancer interaction, or offer new options of radioimmunology. Figure 1 illustrates experimental agents and their targets within the cell cycle. Ongoing clinical trials using agents targeting the immune system-tumor cell interplay are displayed in Figure 2.

Targeting the Epigenome

Modifying DNA Methylation

Decitabine is a cytosine analogue and potent DNA-methyltransferase inhibitor that induces DNA hypomethylation, thus uncovering endogenous retroviral epitopes, which serve as targets for immune attack.[87–89] This effect has been used in cancer with hypermethylated DNA profiles, including AML and MDS.[90] As rhabdoid tumors are an epigenetically driven disease with DNA-methylation-based subtypes (ATRT-TYR and -SHH present DNA-hypermethylation[24]), the use of hypomethylating agents appears to be a promising approach. Retrospective analyses of decitabine in 22 patients with r/r rhabdoid tumors reported radiologic responses in 27% (total n=6, 4= ATRT).[85] Complete remission was achieved in one patient, who received further conventional chemotherapy, while in most patients, response was detected in isolated foci, only. As radiographic response was associated with prolonged time to progression and overall survival,[85] decitabine deserves further evaluation, eg, as bridging therapy in patients with r/r disease. Three current clinical trials employing decitabine in combination with a) immune checkpoint inhibitors (NCT05320640), b) gene-modified T Cells (NCT02650986), and c) a combination with pembrolizumab and hypofractionated radiotherapy (NCT03445858; primary CNS tumors not included) recruit children with solid tumors. Further approaches for children with neuroblastoma, rhabdomyosarcoma, Ewings sarcoma, and osteosarcoma combined decitabine with dendritic cell vaccination (NCT01241162).

Modifying Histone-Methylation

In *SMARCB1* or *SMARCA4* deficient tumors, overexpression of EZH2 leads to increased levels of H3K27me3 in promoter regions of tumor suppressor genes. It is thus a target for EZH2 inhibitors.[91,92] In ATRT, targeted inhibition of EZH2 leads to repression of the Cyclin D1-E2F axis and thus reduced proliferation and apoptosis.[92,93] Moreover, as recently reported, EZH2 deficiency correlates with increased origins of DNA replication in repressed motor regions via H3K27me3 loss.[94]

The orally applicable specific EZH2 inhibitor tazemetostat has been FDA approved for the treatment of inoperable, metastatic epithelioid sarcoma in patients > 16 years.[95] Safety and efficacy have been shown in *SMARCB1*-negative tumors, including ATRT.[96–98] Results from the MATCH study reported prolonged disease stabilization as the best overall

Table 3 Overview of Ongoing Clinical Trials Phases I and II Including Patients with ATRT

Inhibitor Group		Inhibitor	NCT Number	Phase	Study Completion
Immunotherapy	CAR T cells	B7-H3-specific	NCT04185038	I	2041
		C7R-GD2	NCT04099797	I	2039
		HER2-specific	NCT03500991	I	2039
		EGFR806-specific	NCT03638167	I	2040
	Immunovirus therapy	HSV G207	NCT03911388	I	2025
Immune-checkpoint inhibitors	PD-1/CTLA4-Inhibitors	Nivolumab + Ipilimumab + Tazemetostat	NCT05407441*	I/II	2029
	PD-1/CTLA4-Inhibitors	Nivolumab + Ipilimumab	NCT04416568*	II	2025
	PD-L1-Inhibitors	Atezolizumab + Tiragolumab	NCT05286801*	I/II	2025
	PD-1/HDI	Nivolumab + Entinostat	NCT03838042	I/II	2025
Cell cycle inhibitors	CDK4/6 inhibitor	Ribociclib + Gemcitabine Ribociclib + trametinib	NCT03434262	I	2025
		Ribociclib + TOTEM	NCT05429502	I/II	2028
		Abemaciclib (+RT)	NCT02644460	I	2024
		Abemaciclib (+ CTx)	NCT04238819	I/II	2028
		Palbociclib	NCT03709680**	I/II	2025
Targeted therapy	BRD9-degrader	FHD-609	NCT04965753**	I	2025
Targeted tumor cell radiotherapy	Phospholipid drug conjugate	CLR 131	NCT03478462	I	2024
	Radiolabeled monoclonal antibody	Iodine 1131 MOAB 8H9	NCT00089245	I	2025
Protein kinase inhibitor	BCR-ABL tyrosine kinase inhibitor	Dasatinib	NCT00788125	I/II	June 20, 2023
	mTOR inhibitor	Sirolimus	NCT02574728	II	2024
	Aurora Kinase A inhibitor	Alisertib	NCT02114229*	II	2027
Replication	Folic acid analogue	Methotrexate	NCT02905110	Early Phase I	November 2023
Conventional therapy	Conventional chemotherapy, radiotherapy	Risk-adapted therapy	NCT00602667 (infants) NCT00085202 (children)	II	April 2026, December 2023
	HDCT/ASCT, radiotherapy	Controlled, randomized	EudraCT 2018-003335-29*	III	June 2029

Notes: *ATRT exclusive (including rhabdoid tumors, *SMARCB1*-deficient tumors); ***SMARCB1*-deficient tumors focusing on soft tissue tumors.

Abbreviations: AML, acute myeloid leukemia; ASCT, autologous stem cell transplantation; ATRT, atypical teratoid/rhabdoid tumor; CAR T cell, chimeric antigen receptor T cell; CD4T, CD4+ T cell; CDK, cyclin dependent kinase; cfDNA, cell free DNA; CNS, central nervous system; CNV, copy number variations; CRINET, cribriform neuroepithelial tumor; CSF, cerebrospinal fluid; CT, chemotherapy; ctDNA, circulating tumor DNA; CTLA4, cytotoxic T-lymphocyte associated protein 4; DFCI, Dana-Farber Cancer Institute; DIPG, diffuse intrinsic pontine glioma; DNA, desoxyribonucleic acid; DZNep, 3-Deazoplanocin; EED, embryonic ectoderm development; eMRT, extracranial, extrarenal malignant rhabdoid tumor; EU-RHAB, European Rhabdoid Registry; EZH2, enhancer of zeste homolog 2; FDA, Food and Drug Administration; GEMM, genetically engineered mouse model; GLM, germ line mutation; GTR, gross total resection; HDCT, high-dose chemotherapy; HDI, histone deacetylase inhibitor; INI1, integrase interactor 1; IVCT, intraventricular chemotherapy; LGDIT, low grade diffusely infiltrative tumor; M, metastatic; MDM2, murine double minute 2 homolog; MDS, myelodysplastic syndrome; MEK, mitogen-activated protein kinase kinase enzymes; MOAB, monoclonal antibody; MRD, minimal residual disease; MTX, methotrexate; MV-NIS, measles virus (MV) expressing human thyroidal sodium iodide symporter (NIS); oHSV, oncolytic herpes simplex virus; OS, overall survival; PARP, Poly (ADO-ribose) polymerase; PBT, proton beam therapy; PD-1, programmed death protein 1; PD-L1, programmed death ligand 1; PDOX, patient derived orthotopic xenograft; PFS, progression free survival; PR, partial remission; PRC2, polycomb repressive complex; PXA, pleomorphic xanthoastrocytoma; RB, retinoblastoma protein; r/r, recurrent or refractory; RT, radiotherapy; RTK, rhabdoid tumor of the kidney; RTPS, rhabdoid tumor predisposition syndrome; SD, stable disease; SMARCA4, SWI/SNF related matrix associated, actin dependent regulator of chromatin, subfamily a, member 4; SMARCB1, SWI/SNF related matrix associated, actin dependent regulator of chromatin, subfamily b, member 1; SWI/SNF, switch/sucrose non-fermentable; TME, tumor microenvironment; TMB, tumor mutational burden.

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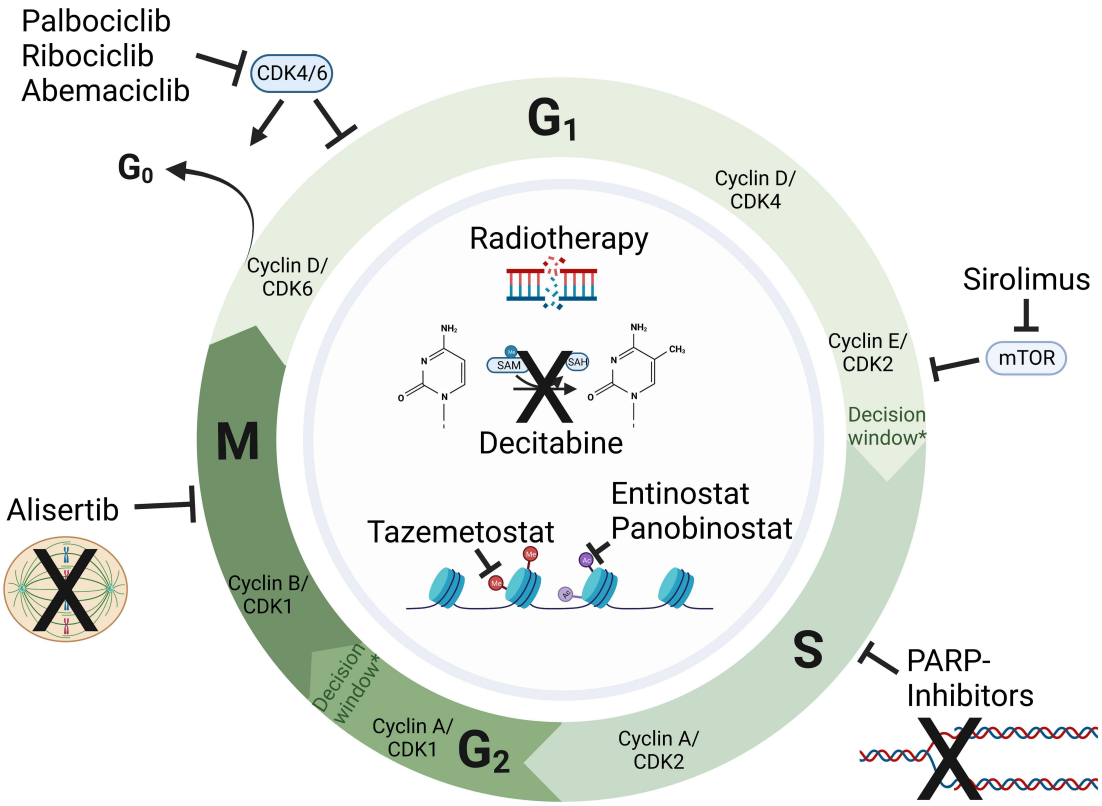

Figure 1 Novel agents for ATRT therapy in clinical phase I and II trials - correlation to the tumor cell cycle. Arrows with even tips indicate "inhibition", arrows with sharp tips indicate "activation", fading arrows with sharp tips indicate "cell cycle exit into G_0 phase". Therapeutic approaches located in the center and surrounded by the grey circle affect more than one distinct phase of the cell cycle in the form of modified gene repression by epigenetically active drugs (decitabine (DNA-hypomethylation), tazemetostat (H3K27me3), entinostat and panobinostat (HDACI)), or DNA damage dependent cell cycle exit in G_1 and G_2 (radiotherapy induced double strand breaks). *Reaching and passing decision windows is driven by appropriate cyclin/CDK levels: G_1/S transition is regulated by Cyclin D/CDK2/4/6, while Cyclin A/B/CDK1/2 affect G_2/M transition.[86] A mitotic entry commitment point, a mitotic exit commitment point, or a S phase entry commitment point regulated by DNA damage, DNA replication stress, or spindle assessment are not shown in this figure. Created with Biorender.com.

response in 1 of 8 ATRT (13.7 months PFS) with confirmed loss-of-function alterations in the *SMARCB1* gene.[99] Ongoing clinical trials investigate the safety and efficacy of tazemetostat, as a single agent (NCT02601950) or in combinatorial approaches (NCT04537715, NCT05407441). NCT05407441 investigating the combination of tazemetostat with the immune-checkpoint inhibitors nivolumab (PD1 inhibitor) and ipilimumab (CTLA4 inhibitor) in INI1-negative/*SMARCA4*-deficient tumors has recently opened recruitment (estimated study completion 02/2029). Prescribing tazemetostat needs to consider the risk of development of secondary lymphoma described by Chi et al[96] as well as the development of drug resistance.[100] Trying to explain underlying mechanisms, Shinohara et al reported an increased expression of the EZH2 homologue EZH1 by depletion or chemical inhibition of EZH2 in cell lines and mouse xenograft models of rhabdoid tumors. These authors suggested decreased or repressed EZH2 levels as a cause for overexpression of EZH1, which in turn compensates the loss of function of EZH2. Targeting both EZH1 and EZH2, reduced H3K27me3 accumulation (in *CDKN2A*) as well as cell growth control.[101] More recently, Kazansky et al proposed combined epigenetic therapy to overcome clinical resistance to EZH2 inhibition. The authors provide potential key requirements for the effective use of tazemetostat in *SMARCB1*-deficient tumors: (1) Intactness of drug binding sites of EZH2 and subsequent pathway components (including transcription factors and co-activators). This means that chromatin remodeling complexes must act on tumor suppressor loci that were aberrantly repressed by PRC2, and these must be upregulated for a response to tazemetostat. For example, mutations in *CDKN2A* and *CDKN2B* will lead to decreased *RB1* activation and subsequent reduced cell cycle inhibition at G1/S transition. 2. Targeting the non-enzymatic core PRC2 subunit EED, as well as combining additional drugs affecting the cell cycle beyond the G_1/S checkpoint, could help overcome tazemetostat resistance.[84]

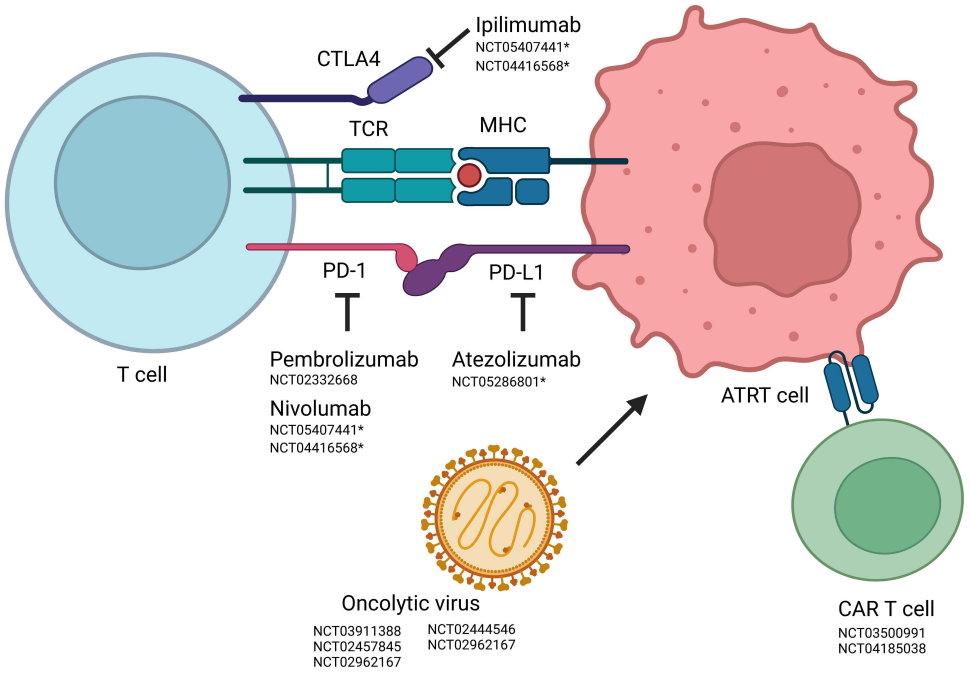

Figure 2 Novel targets affecting the interaction between ATRT tumor cells and the immune system. Structures investigated in clinical phase I and II trials targeting the interaction of T and ATRT tumor cells. Current clinical trials are provided for each agent in form of the NCT identifier. Trials including *SMARCB1*/*SMARCA4*-deficient entities only (focus on ATRT) are highlighted with *. Arrows with even tips indicate "inhibition", arrows with sharp tips "uptake in". Created with Biorender.com.
Abbreviations: CTLA4, cytotoxic T-lymphocyte-associated protein 4; TCR, T cell receptor; MHC, major histocompatibility complex; PD-1, programmed death protein 1; PD-L1, programmed death ligand 1.

Intratumor heterogeneity may provide a further explanation for drug resistance, as Qi et al supposed when describing regions of repressed EZH2 in residual tumors. It cannot be determined whether this induces or is affected by therapy resistance.[102]

Modifying Histone Acetylation

Recent data indicate the effect of panobinostat on histone-H4 acetylation leading to encouraging treatment stabilization when used as maintenance therapy.[103] Results of a current trial are pending, and the first-line pre-treatment is likely to substantially affect treatment response. INFORM 2 employs the histone-deacetylase inhibitor entinostat in combination with the immune checkpoint inhibitor nivolumab (NCT03838042, including ATRT).

Tyrosine Kinase Inhibition

Aurora Kinase A Inhibitors

The aurora kinase A inhibitor alisertib leads to impairment of mitotic spindle assembly (as reviewed in[104]). A phase II study (SJATRT) investigated a cohort of rhabdoid tumors. Results for stratum A1 (recurrent or progressive ATRT) were published in 2023: Intermittent objective responses to treatment were achieved in 9/30 patients (n=8 stable disease (SD), n=1 partial remission (PR) in the 12-week assessment). A total of 25 patients eventually developed progressive disease. Five patients achieved a follow-up time of more than 50 weeks (4/5 ATRT-TYR, 1/5 ATRT-MYC, all > 1 year of age at enrolment). It should be stressed that two of them received alisertib for less than 2 months and never responded to treatment. All survivors received further salvage therapy. The authors suggest a potential role of alisertib in bridging or palliative care, only.[105] Anecdotally, long time remission for 3 years following alisertib was reported in an infant with ATRT-TYR in the treatment of its 2nd relapse.[106]

BCR-ABL Tyrosine Kinase Inhibitor

The BCR-ABL tyrosine kinase inhibitor dasatinib was developed for the treatment of Philadelphia-chromosome-positive leukaemia[107] and investigated in a phase I/II clinical trial (NCT00788235) in children with metastatic or recurrent

malignant solid tumors including brain tumors as part of a combined anti-cancer treatment approach. According to the results published on *clinicaltrials.gov*, 6 out of 7 patients did not complete protocol treatment and succumbed due to disease (https://clinicaltrials.gov/study/NCT00788125?term=NCT00788125&rank=1andtab=results; no information on actually included tumor types, ATRT not an exclusion criterion).

Targeting the CDK4/6/Cyclin D/RB Pathway

During the early G_1 phase, increased levels of Cyclin D as well as Cyclin-dependent Kinases (CDK) 4 and 6 are needed to maintain the cell cycle and to prevent cell cycle exit (as reviewed in[86]). Targeting CDK4/6 inhibitors aims at inducing cell cycle arrest in G_0/G_1 before reaching the G_1/S decision window.

Ribociclib penetrates the blood–brain barrier and is thus an interesting drug in CNS tumors.[108] Clinical phase I trials report weak therapeutic success. In 2017, a phase I trial demonstrated the safety of CDK4/6 inhibitors, but best overall response was stable disease in 2 of 13 patients with recurrent ATRT.[109] Recently published data report no objective responses in 18 children with recurrent or refractory malignant CNS tumors (no ATRT included) treated with a combination of ribociclib and everolimus. All patients, who completed follow-up, experienced disease progression.[110] Investigating cell lines of adult CNS tumors, the combination of CDK4/6 inhibitors and other commonly used cytotoxic anti-neoplastic drugs could not provide any enhanced therapeutic success, as Jin et al reported in 2019.[111] Disease stabilization over a period of 32 to 48 weeks, as described by Geoerger et al,[109] still represents a remarkable achievement in the treatment of recurrent or relapsed ATRT.

The ongoing clinical trials NCT03434262 and NCT05429502 evaluate ribociclib as part of a combination therapy (combining with nucleoside analogues, inhibitors of the Hedgehog pathway, MEK inhibitors, or commonly used cytotoxic antineoplastic drugs such as topotecan and temozolomide (TOTEM)).

The phase I/II trial NCT02644460 evaluated abemaciclib as a single agent in children with CNS tumors and especially DIPG (ATRT not excluded) NCT04238819 (ATRT not excluded) looked into a combination with other anti-cancer treatment in pediatric patients with relapsed and refractory solid tumors.

Data from the Pediatric Brain Tumor Consortium study PBTC-042 investigating palbociclib as a single agent in patients with progressive CNS tumors showed limited treatment response, as none of the tumors responded and up to 90% progressed on treatment, although 80% of the tumors were tested positive for *RB* status before initiating treatment.[112] A phase I/II study currently investigated palbociclib combined with chemotherapy (irinotecan, topotecan, temozolomide, or cyclophosphamide) in children with recurrent or refractory solid tumors including eMRT (NCT03709680).

PARP-Inhibitors and DNA-Repair

Poly(ADP-ribose) polymeraseS (PARPS) are multifunctional enzymes involved in DNA damage repair and maintaining genome stability. DNA damage leads to recruitment of PARP and DNA repair enzymes. PARP inhibitors prevent dissociation of the PARP-complex off the DNA strand thus inducing replication fork collapse.[113,114]

Preclinical trials found decreased cell growth, reduced colony formation, cell cycle arrest, and apoptosis due to accumulation of DNA damage in the ATRT cell lines BT16 and MAF37 following treatment with the PARP inhibitor rucaparib. Prolonged survival in xenografted mice and potential synergistic effects increasing radiosensitivity suggest a potential therapeutic use.[113] Until this day, there is no clinical trial confirming the pre-clinical effect of PARP inhibitors in ATRT, or rhabdoid tumors in general. However, the safety of the PARP inhibitors niraparib, talazoparib, and olaparib is under investigation in clinical trials NCT04544995 (no CNS-Tumors, eMRT not excluded), NCT023492793 (published for Ewing sarcoma, no objective response),[115] and NCT01858168 (Ewing sarcoma and rhabdomyosarcoma), respectively. Despite dismal treatment responses upon single agent use, recent investigations in pediatric solid tumors provide information on beneficial effects of PARP inhibitors combined with conventional chemotherapy, ie, alkylating agents or topoisomerase inhibitors.[116]

Immunotherapy Approaches

Tumor immune microenvironment (TME) modulation is a successful approach in cancer treatment.[117] Grabovska et al described immune cell infiltration in multiple pediatric brain tumors, including 229 ATRT and demonstrated distinct

immune cell infiltration profiles in the three ATRT subtypes (ATRT-MYC: CD8T, monocytes, Treg, B-cells, eosinophils; ATRT-SHH: CD8T, Treg, B-cells, monocytes, eosinophils; ATRT-TYR: Treg, B-cells, monocytes, eosinophils, NK cells, CD4T, neutrophils). The ATRT-TYR subgroup demonstrated infiltrations with NK- and CD4T-cells, which were neither found in ATRT-MYC nor -SHH.[118] Several approaches integrating modulation of the TME in ATRT management have been developed (see Table 3).

Immune Checkpoint Inhibitors

Programmed death protein-1 (PD-1), programmed death ligand 1 (PD-L1) and cytotoxic T-lymphocyte associated protein 4 (CTLA4) are part of the tumor cell immune escape, as T cell mediated immune response is downregulated by PD-1-PD-L1 interaction[117] or by activating CTLA4 (reviewed in[119]). Immune Checkpoint inhibitors block PD-1, PD-L1, or CTLA4 to sustain T cell mediated immune response against tumor cells.

The PD-1 inhibitor pembrolizumab has shown encouraging responses (partial response) in patients with confirmed PD-L1 expression in the tumor tissue, including 1 eMRT. Albeit PD-1 expression was confirmed in 95% of cases, 72% experienced progressive disease while on treatment. ATRT was not included in this investigation (NCT02332668).[120] Similar results were described for the PD-1 inhibitor nivolumab in a cohort of recurrent or refractory pediatric CNS tumors: transient radiographic responses were seen in 30%. Disease progression was found in all patients but occurred earlier in patients with negative PD-L1 expression compared to patients with positive PD-L1 expression (not statistically significant). The investigators suggest there might be a correlation between tumor mutation burden (TMB) and response to immune checkpoint inhibitors since nivolumab reached best efficacy in the patient with highest TMB.[121]

In a phase I/II study, the PD-L1 inhibitor atezolizumab elicited an objective response in 1 of 6 patients with relapsed extracranial malignant rhabdoid tumors. This patient exhibited high PD-L1 expression and experienced several months without tumor progression. eMRT with no or low PD-L1 expression did not respond to atezolizumab treatment.[122] This effect has yet to be confirmed in ATRT and is under investigation in an ongoing clinical trial (NCT05286801, including ATRT) in a combined drug approach including tiragolumab.

Ongoing clinical trials in r/r high-risk pediatric cancer investigating immune checkpoint inhibitors in pediatric *SMARCB1*-deficient tumors mainly focus on the PD-1 inhibitor nivolumab in combination with the CLTA4 inhibitor ipilimumab with or without tazemetostat (NCT05407441, NCT04416568, both including ATRT), as well as in combination with the HDI entinostat (NCT03838042, including ATRT).

CAR T-Cells

Chimeric antigen receptor (CAR) T cells may target the epitopes of B7-H3, C7R-GD2, HER2, and EGFR806, which are specifically or highly overexpressed on CNS tumor cell surfaces.[123] Target selection has been predominantly driven by expression in adult glioblastoma.[124]

Safety and feasibility of locoregional infusion of HER2-specific CAR T cells have been demonstrated in recurrent or refractory adult and pediatric CNS tumors (NCT03500991, including ATRT). Repeated administration of HER2-specific CAR T cells either into the tumor cavity or the ventricular system was safe in the first three patients enrolled. Immune activation was measured in the form of elevated cytokine (eg, CXCL10 and CCL2) levels in the cerebrospinal fluid (CSF).[125] However, assessment of treatment response and further safety profiles are not yet available.

B7-H3 is elevated in ATRT.[123] Following CAR T cell treatment, ATRT xenografted mice revealed a tumor cell purging effect.[126] Safety and efficacy of B7-H3-specific CAR T cells in children are currently being investigated in a phase I clinical trial (NCT04185038, including ATRT). Published results of three patients with DIPG showed the feasibility and safety of intraventricular B7-H3-specific CAR T cell administration in children with CNS tumors, with one patient providing a radiographic response for more than 12 months.[127]

Glioblastomas mainly express EGFR806[128] and has been employed as a target in clinical phase I trial NCT03638167 for recurrent or relapsed pediatric brain tumors, including ATRT.

Radioimmunotherapy

In addition to being a target for CAR-T-cells B7H3 serves as a target for immunolabeled radioligands. Employing the radiolabeled monoclonal antibody ^{131}I-omburtamab, a radiation source can be directed at B7H3 expressing cells. A phase

I trial in children with recurrent CNS malignancies including one ATRT infused ^{131}I-omburtamab into the ventricles. The radioactive compound barely passed the blood–brain barrier and exposure to organs at risk was low. Patients suffering from neuroblastomas experienced improved survival, while neither tumor remission nor prolonged disease stabilization was reached for the only patient with ATRT.[129] Ongoing clinical phase I trials such as NCT03478462 and NCT00089245 investigate the I-131 monoclonal antibody 8H9 and CLR 131 in children with recurrent CNS malignancies (ATRT not excluded).

Immunovirus Therapy

Modified oncolytic Herpes simplex virus-1 (oHSV-1) is capable of selectively infecting tumor cells with lasting responses. Antiviral treatment is employed as a safety insurance for healthy tissue. Anti-tumor effects are based on virus-induced oncolysis and stimulated anti-tumor immune responses. Cell surface structures including nectin (CD-111), expressed on CNS tumor cells, enable oHSV to attach to and enter tumor cells specifically.[130] It has been shown that the oHSV subtype G207 is able to switch the tumor microenvironment from immunological "cold" to "hot" by increasing lymphocyte infiltration. A phase I study of genetically engineered herpes simplex virus (HSV G207) has started in 2020 (NCT03911388). Due to a biallelic deletion of the neurovirulent gene $\gamma_1$34.5 and insertion of the reporter *lacZ* into the U_l39 gene, which encodes ribonucleotide reductase inactivating ICP6,[131] G207 is assumed to be non-neurovirulent, replication competent and selectively oncolytic. Safety of G207 was investigated in animal models and clinical trials recruiting adult patients. Importantly, a phase I trial, investigating G207 in pediatric malignant supratentorial tumors (glioblastoma, anaplastic astrocytoma; NCT02457845) showed convincing safety profiles and radiographic, neuropathological, or clinical response in 11 of 12 patients.[132] An ongoing phase I trial investigates G207 in pediatric cerebellar tumors (not excluding ATRT).[133]

Modified Oncolytic reovirus and measles virus have been investigated in recently completed clinical trials in ATRT (NCT02444546, NCT02962167). Wild-type reovirus was administered in combination with sargramostim in young patients with high-grade r/r CNS tumors (NCT0244546). In this trial, all patients (no ATRT thus far) experienced tumor progression and death of disease.[134] In the clinical phase I trial NCT02962167, modified measles virus (MV-NIS) was administered in patients with recurrent medulloblastoma or ATRT, either directly into the tumor bed during standard of care tumor resection or via lumbar puncture depending on tumor dissemination (results are pending). Oncolytic measles virus selectively infects cells with high CD46 surface expression, eg, tumor cells. CD46 is part of the complement inactivation system and therefore involved in tumor immune escape.[130,135–137] The oncolytic effect of reoviruses is caused by tumor cell overexpression of Ras enabling active viral dsRNA translation, which is blocked in normal tissue cells.[130,138]

Synthetic Lethality

Most novel therapeutic approaches in ATRT aim to inhibit overexpressed gene products. Due to the pronounced stability of the ATRT genome, the number of potential targets is limited. Identification of additional crucial gene products, eg, in the context of synthetic lethality, may present another approach to overcome therapeutic limitations. Synthetic lethality can be defined as lethality of cells or organisms caused by combined alterations of gene pairs, with single alterations in both maintaining viability.[139] CRISPR-Cas-9 screens identified *BRD9*, a subunit of the non-canonical *SWI/SNF* complex, as a potential target for synthetic lethality. In *SMARCB1*-deficient rhabdoid tumor cell lines *BRD9* knock-out decreased cell proliferation and viability.[140,141] Clinical approaches evaluate the feasibility of the molecular *BRD9* degrader FHD-609 in adult and older pediatric (>16 years) patients with *SMARCB1*-deficient tumors (NCT04965753).

Preclinical Approaches to Increase Radiosensitivity

Histone Modifications Increase Radiosensitivity

Preclinical experiments attempt to induce radiation sensitivity by inhibition of histone modifying enzymes. EZH2 inhibition and treatment with the unspecific inhibitor of histone methylation DZNep increased the vulnerability of ATRT cell lines to radiotherapy. This finding is likely due to a general restriction of DNA synthesis and cell cycle progression by affecting EF2/c-Myc and Cyclin D1/CDK6/c-Myc/RB pathways caused by targeted molecular inhibition

(shRNA) of EZH2 and the S-adenosylhomocysteine hydrolase inhibitor DZNep, which induces apoptosis and cell cycle arrest in ATRT cell lines.[92] We would like to point out that EZH2 inhibition by tazemetostat cannot match inhibition using CRISPR CAS9 or shRNA, as the latter is much more efficient. In patient-derived orthotopic xenograft mouse models, it was demonstrated that tazemetostat significantly prolonged survival compared to non-tazemetostat, but did not improve responses to RT.[102] Therefore, in vivo effects were less obvious than anticipated from experimental investigations.

Histone deacetylase inhibitors (HDI) effects on apoptosis and cell cycle arrest may be explained by induction of p21 transcription by HDI SNDX-275.[142] The HDI entinostat (SNDX-275), was safe in a recently completed phase I trial (NCT02780804), which included refractory primary CNS tumors (no ATRT), while response to treatment was weak, as 20 of 21 patients experienced progression within the first 3 courses. Only one patient with ependymoma reached a stable disease following 28 courses.[143] The currently recruiting INFORM2 (NivEnt) trial for refractory malignancies including primary CNS tumors combines entinostat and the PD-1 inhibitor nivolumab. An arm for patients with ATRT below 6 years of age is anticipated to open once an orally available formulation for entinostat can be provided.

Induction of Proapoptotic Pathways

Small-molecule MDM2 inhibitors such as nutlin 3 and idasanutlin activate the proapoptotic *TP53* pathway and increase the effect of radiation-induced DNA damage in ATRT in vitro.

Consistently combining idasanutlin with irradiation significantly reduced proliferation in ATRT cell lines.[144] A corresponding radiographic response was shown in orthotopic xenograft mouse models treated with idasanutlin including intratumor necrosis.[144] Further studies are needed to assess therapeutic success in clinical settings.

Future Directions – Discussion and Outlook

Within this review, we have given examples of the biological and clinical heterogeneity of ATRT and the associated challenges in therapy. Despite crucial improvements in therapeutic modalities and understanding of the molecular biology of ATRT results from clinical trials suggest that prognosis depends mainly on clinical characteristics such as age, metastatic disease, GLM, and extent of surgery. First attempts to classify risk groups, eg, ATRT-TYR as a positive predictor deserve further validation in a prospective fashion.

Treatment of relapsed and refractory ATRT remains an enormous challenge as single agents have not yet yielded any convincing responses in the limited number of phase I/II trials. We thus suggest that innovative, personalized treatment strategies need to include aspects of intra- and intertumoral heterogeneity. Such approaches, especially in r/r ATRT, need to respect clinical aspects including age at diagnosis and metastatic status. These will likely significantly influence the intensity and extent of conventional treatment elements (eg, fields of re-radiotherapy). Furthermore, molecular features such as genetic or epigenetic characteristics will guide individualized treatment approaches.

Rational drug combinations bear the potential to potentiate the therapeutic effects of single agents. Combinatorial approaches are currently investigated, eg, for immune checkpoint inhibitors and EZH2 inhibitors but also HDI (NCT05407441, NCT04416568, NCT05286801, and NCT03838042).

A potential model for therapeutic decision is given in Figure 3. As knowledge increases rapidly, every model certainly warrants constant re-evaluation and adaptation.

The Challenge of Treating r/r ATRT

Despite first data that methylation subgroups may have prognostic significance, there remains a dearth of validated, reliable, and potent biomarkers predicting treatment response in general but also to specific targeting agents.

Several attempts have been made to correlate clinical and molecular characteristics with clinical outcome.[4,30,32] First steps involving machine learning and artificial intelligence methods to generate prognostic algorithms have been initiated.[145] As this has identified prognostic treatment elements such as the extent of surgery, radiotherapy, and chemotherapy, it reproduces more or less the current knowledge obtained from retrospective analyses. We need to acknowledge these attempts as proof-of-principle approaches, which build the basis for improved and more complex AI models. These are anxiously awaited.

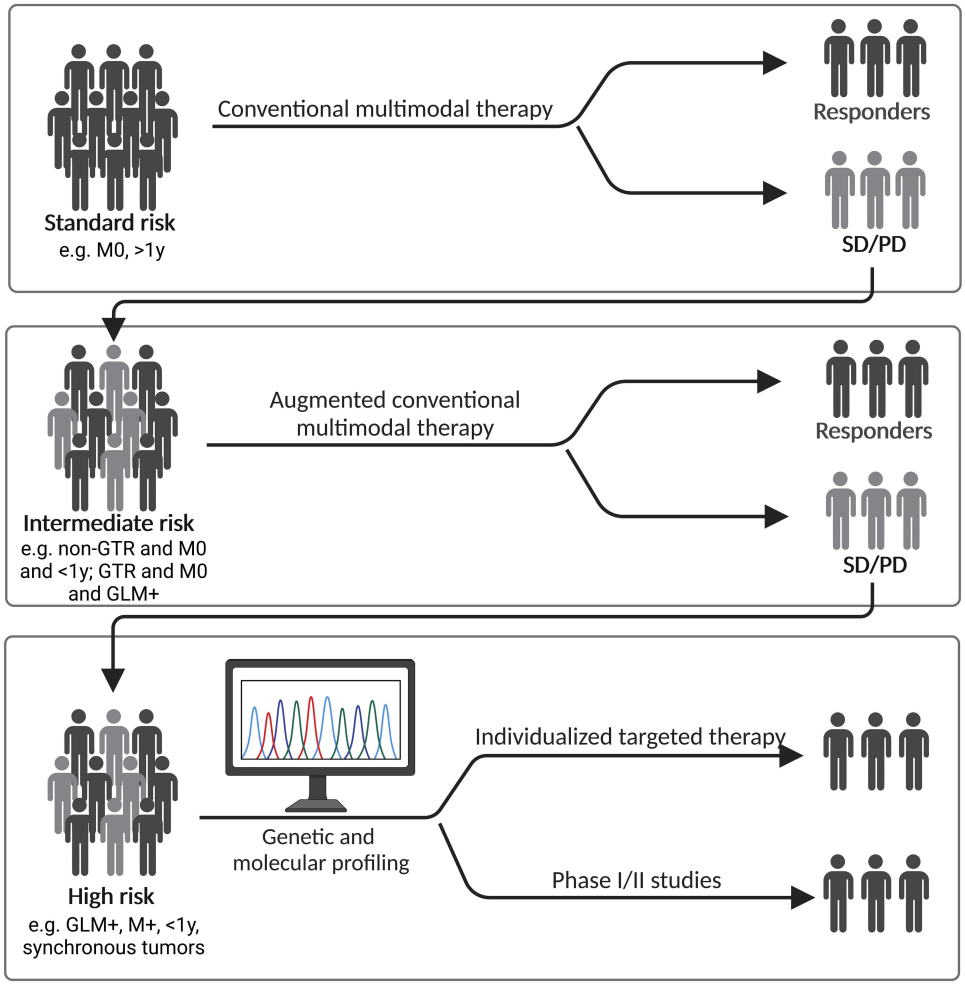

Figure 3 Risk factor-based model for treatment decision in ATRT. For standard risk patients, multimodal conventional therapy is the first line choice. Patients not achieving an objective response (SD, stable disease) and non-responders (PD, progressive disease) will be re-stratified into an intermediate risk group. Treatment of intermediate risk patients may add individual or combined novel targeting agents to conventional therapy. Delayed (SD) and non-responders (PD) will drop to a high-risk stratum. Treatment in the high-risk stratum will be individualized based on genetic and molecular profiling, and/or patients will be included in phase I/II clinical basket trials. Black characters represent responders, grey characters non-responders to current or previous treatment. Exemplary risk factors are provided for potential stratification and have to be defined by further research in form of international meta-analysis. Created with Biorender.com.
Abbreviations: GLM, germ line mutation; GTR, gross total resection; M, metastasis; y, year of age at diagnosis.

Treatment Adjustments – The Role of Molecular Subgroups

In 2020 we agreed on a consensus classification of ATRT into three separate molecular groups, each characterized by distinct clinical, molecular, and genetic characteristics. We suggest that divergent gene expression profiles[27] may be responsible for the heterogeneous response to conventional but also potential targeted therapy approaches. Recently, Johann and Altendorf elucidated distinct gene expression profiles in primary vs relapsed ATRT. For ATRT-MYC, differences were seen in the expression of cell cycle-dependent genes (eg, HDAC), while gene coding for components of the immune system was more likely to be downregulated in relapse compared to primaries. Tyrosine kinase receptor genes were overexpressed in relapse in ATRT-TYR tumors, while ATRT-SHH relapse displayed higher expression of genes associated with metastases.[146]

Paassen et al developed a series of ATRT tumoroids and performed extensive drug screening. In contrast to suggestions by Altendorf et al, tyrosine kinase inhibitors were significantly more effective in ATRT-MYC tumoroids when compared to ATRT-SHH. For ATRT-SHH, gamma-secretase inhibitors affecting the NOTCH-pathway were most successful, even though differences between the different ATRT-SHH models were detected.[147] We would like to stress that different gene expression profiles of the distinct DNA methylation groups will likely play a crucial role for targeted

treatment approaches. Results from current studies will need to be confirmed in larger cohorts. Eventually clinical trials investigating novel therapeutic agents should correlate specifics of molecular subgroups with clinical data.

Improvements in the Diagnostic Workup

It remains to be determined whether our diagnostic portfolio is efficient enough to define treatment responses and, even more importantly, to detect relapse early. Standard of care surveillance methods mainly comprise MRI screens and occasionally CSF cytology, both demonstrating significant inter-examiner variability.

Ideally, diagnostic methods with a high specificity and sensitivity will enhance the screening for minimal residual disease (MRD) currently invisible to the human eye. Detecting cell free DNA (cfDNA) in body fluids reflects current attempts to gather diagnostic information by a non- or minimally invasive and technically standardizable system. These liquid biopsies will complement future diagnostic surveillance and initial workup. Such approaches have been investigated in different specimens. Sample volume and amount of DNA per volume have to be considered when designing experimental analyses. In the CSF of patients with CNS tumors, the amount of cfDNA is generally low. It appears to be significantly higher compared to serum/plasma, even though the absolute amount of DNA remains limited.[148] Nanopore sequencing has recently been shown to be an easy-to-use and reliable method to detect even small amounts of DNA in limited sample volumes.[149–151] Nanopore provides a membrane-based whole sequencing approach without the need for polymerase-based amplification.[149–153] Copy number variations (CNV) and DNA methylation profiles may be generated at the same time from the same sample.[153] Data by Afflerbach et al demonstrated encouraging success in detecting amounts of 5 ng of circulating cell free DNA in CSF volumes as little as 1 mL. These investigators were able to show that cfDNA was indeed circulating tumor DNA (ctDNA), as they presented identical CNV and DNA methylation patterns as in the tumor tissue. This was validated in eight patients suffering from ATRT. These methods were considered appropriate for the detection of ctDNA in pre-operatively collected CSF as well as in the longitudinal disease monitoring.[153]

In summary, several lines of evidence demonstrate that liquid biopsy may be a suitable tool for MRD detection especially in high grade (embryonal) CNS tumors as 1) the amount of ctDNA is higher than in CNS tumors of lower grade and 2) a CSF access device (eg, Ommaya or Rickham) will be placed for intraventricular therapy in the first-line treatment.[148,153] We anticipate a high potential for the establishment of liquid biopsies from ventricular reservoir CSF in patients with ATRT. Collecting samples within the scope of clinical trials may further be considered but requires a standardized procedure for both specimen collection and storage as well as laboratory analyses.

Preclinical Evaluation of Potential Novel Therapies

Traditionally, animal models have been an important tool for drug testing. ATRT animal models, most commonly immune-incompetent mice for xenografts or genetically engineered mouse models (GEMM), appear to be rather limited.[154,155] Currently available models do not exactly recapitulate ATRT biology, eg, the models published by Roberts et al demonstrate rather long generation times and CNS tumors are rarely seen,[156] xenograft tumors exhibit an incomplete tumor immune infiltration due to the generation in nude mice and even the GEMM such as the one published by Han or Melcher do not give a perfect representation of the established methylation subtypes.[155,157]

As an alternative to animal models, attempts have been made to create tumoroids based on patient-derived tumor samples or patient-derived orthotopic xenografts (PDOX). Paassen et al developed such tumoroid models and demonstrated the potential use in pre-clinical research, as these models are presented with stable genetic and epigenetic characteristics despite several cycles of tumor cell passage and expansion in cell culture.[147] Even if these authors used minced tumor tissue,[147] consisting of tumor cells and tumor microenvironment, these tumoroids are still not a perfect representation of the primary tissue. This may be explained by the lack of our knowledge on how to produce the 3-dimensional architecture within tumoroid models. Developing innovative tumor models will have to respect the spatial geometry of ATRT.

Outlook

Future research needs to focus on a correlation of molecular and genetic structures with response to treatment. This will be crucial to provide the best possible treatment for each patient, to design meaningful clinical trials, and to eventually improve survival.

Trial designs face the challenge of requirements for randomized controlled clinical trials to gather as much evidence as possible on the one hand, and individual genetic and molecular findings on the other small subcohorts of patients. International knowledge must be merged in common databases to overcome limited cohort sizes and to achieve maximum possible evidence.

Conclusion

Conventional, multimodal therapy in ATRT deserves further optimization. Regardless of the treatment approach, risk factors such as age, metastatic disease, and GLM affect survival probability. The clinical benefit and the risk of severe acute and late effects, especially in young children, stress the necessity to modify radiotherapy approaches. Proton beam therapy may cause less severe late effects and may therefore be an option in children younger than 18 months. It has been proposed that HDCT may replace radiotherapy; this issue remains unresolved.

While specific, mostly institutional approaches for the treatment of primary ATRT exist, the management of refractory and relapsed ATRT in general follows clinical phase I/II trials or individual treatment attempts. Agents under investigation include CDK4/6, PARP, or aurora kinase a inhibitors. Others belong to the group of epigenome modifying compounds (such as decitabine, or histone modifying agents). Inhibition of the PD-1/PD-L1 interaction or T cell activation via CTLA4 blockade targets the tumor cell directed immune responses. CAR-T-cells or oncolytic viruses are additional immune modulating agents. Recent basket trials to individualize targeted therapy based on expression profiles still face the difficulty of identifying reliable and targetable structures.

We suggest that a research-informed combinations of agents will improve treatment response in primary as well as r/r ATRT. Crucially, merging global knowledge in the form of internationally recruiting trials or meta-analyses is an important approach to reach significant numbers by building efficient collaborative networks.

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