Cancer Treatment Reviews 136 (2025) 102942

Contents lists available at ScienceDirect

Cancer Treatment Reviews

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

Targeting pediatric adrenocortical carcinoma: Molecular insights and emerging therapeutic strategies

Michaela Kuhlen [a,b,*], Maximilian Schmutz [c], Marina Kunstreich [a,d], Antje Redlich [d], Rainer Claus [b,e]

[a] Pediatrics and Adolescent Medicine, Faculty of Medicine, University of Augsburg, Stenglinstr. 2, 86156 Augsburg, Germany
[b] Bavarian Cancer Research Center (BZKF), Augsburg, Germany
[c] Hematology and Oncology, Faculty of Medicine, University of Augsburg, Stenglinstr. 2, 86156 Augsburg, Germany
[d] Department of Pediatrics, Pediatric Hematology/Oncology, Otto-von-Guericke-University, Leipziger Str. 44, 39120 Magdeburg, Germany
[e] Pathology, Faculty of Medicine, University of Augsburg, Stenglinstr. 2, 86156 Augsburg, Germany

ARTICLE INFO

Keywords:
Children and adolescents
Adrenocortical carcinoma
Therapy
Overview

ABSTRACT

Pediatric adrenocortical carcinoma (pACC) is an exceptionally rare and aggressive malignancy, accounting for only 0.2–0.3% of childhood cancers. Characterized by significant endocrine activity and often associated with genetic syndromes such as Li-Fraumeni syndrome, pACC exhibits distinct clinical and molecular profiles compared to adult adrenocortical carcinoma (ACC). Current treatment approaches, largely adapted from adult protocols, center on surgery and chemotherapy, including mitotane. However, the lack of pediatric-specific data and major clinical trials underscores a pressing need for tailored therapeutic strategies.

Advances in molecular profiling have unveiled actionable targets, such as alterations in the Wnt/β-catenin and MAP/ERK pathways, overexpression of IGF2, and epigenetic dysregulation. Emerging therapies, including immune checkpoint inhibitors, CAR T-cell therapy, and radiopharmaceuticals, hold promise but remain largely untested in pediatric populations. Targeting metabolic vulnerabilities, such as steroidogenesis and lipid metabolism, offers additional avenues for therapeutic innovation. Furthermore, improved diagnostic tools like liquid biopsy and steroid profiling may enhance disease monitoring and early detection.

Despite progress in understanding pACC biology, significant challenges remain in translating these insights into effective treatments. Collaborative efforts, such as the European Cooperative Study Group for Pediatric Rare Tumors (EXPeRT), and the development of pediatric-specific clinical trials are vital for advancing the field. Multidisciplinary care and international research initiatives will be pivotal in addressing the unmet needs of pACC patients.

By leveraging molecular insights and fostering global collaboration, the field can move toward personalized medicine, improving outcomes and quality of life for children with this challenging disease. Expanding clinical trials, refining diagnostic tools, and integrating novel therapies into treatment regimens will be critical in bridging the gap between pediatric and adult ACC treatment success.

Pediatric adrenocortical carcinoma — A rare and unique entity

Pediatric adrenocortical tumors (pACTs) are a spectrum of neoplasms originating from the adrenal cortex, ranging from benign adenomas to carcinomas [1,2]. Among these, pediatric adrenocortical carcinoma (pACC) is an exceptionally rare and aggressive malignancy, accounting for just 0.2–0.3 % of childhood cancers, with an incidence of 0.3–0.7 cases per million children annually [3,4].

pACC shows two distinct age-related peaks: early childhood (before age 4) and adolescence, with a marked female predominance [3,5–7]. A hallmark feature is excessive steroid hormone secretion (cortisol, aldosterone, androgens, estrogens), leading to clinical manifestations like virilization and Cushing syndrome [5,7,8].

Genetic predisposition is pivotal in pACC pathogenesis, with ~ 60 % of cases linked to syndromes such as Li-Fraumeni (LFS) and Beckwith-Wiedemann (BWS) [9,10].

Complete surgical resection remains the primary treatment and key prognostic factor [2,7,11,12]. In advanced disease stages, including

* Corresponding author at: Pediatrics and Adolescent Medicine, Faculty of Medicine, University of Augsburg, Stenglinstr. 2, 86156 Augsburg, Germany.
E-mail address: Michaela.Kuhlen@uk-augsburg.de (M. Kuhlen).

https://doi.org/10.1016/j.ctrv.2025.102942
Received 18 January 2025; Received in revised form 15 April 2025; Accepted 15 April 2025
Available online 16 April 2025

stage III, stage IV tumors, and unresectable disease, (neo)adjuvant or palliative therapies, including chemotherapy and mitotane, show limited efficacy with 5-year survival rates of 20–50 % which highlights the urgent need for novel, effective therapies [2,3,11,13–15].

The rarity of pACC poses a major challenge, as evidence from treatment trials is limited; phase III data are almost entirely lacking and unlikely to emerge. Thus, pACC may serve as a model disease for very rare cancers, where mechanistic understanding can guide therapeutic strategies despite the absence of high-level clinical evidence. Deep molecular insights inform urgently needed improvements in therapy, not only for pACC but also for other rare and difficult-to-treat cancers lacking standardized treatment approaches [16].

Molecular and genetic insights

Molecular subgroups

Pinto et al. identified common tumorigenic mechanisms in 37 pACTs, including overexpression of insulin-like growth factor 2 (*IGF2*), dysregulation of the Wnt/ß-catenin pathway (*CTNNB1*), and telomere maintenance dysfunction via *ATRX* mutations [17] (Fig. 1).

These findings delineate molecular subgroups defined by specific genetic alterations driving tumor development and progression. The primary alterations include:

***TP53* mutations**: Germline *TP53* mutations are found in a high proportion of pACC cases, [17] particularly in children under age 12, with reported rates of 50 %-80 %. This frequency drops to 25 % in patients aged 12–20 years [10]. Additionally, somatic *TP53* mutations occur in ~ 25 % of tumors with wild-type germline *TP53* [17]. *TP53* plays a pivotal role in cell cycle regulation and tumor suppression.

***ATRX* mutations**: Somatic *ATRX* mutations, identified in 32 % of ACTs, are exclusively associated with germline *TP53* mutations. *ATRX* encodes a helicase involved in chromatin remodeling and telomere maintenance.

β-Catenin activation: *CTNNB1* mutations are present in ~ 18 % of pACTs, leading to dysregulated Wnt/β-catenin signaling. These mutations are only seen in tumors with wild-type germline *TP53*.

Based on these alterations, Pinto et al. [17] classified pACTs into three molecular subgroups, with Group 1 showing significant poorer survival compared to Groups 2 and 3:

Group 1: Germline *TP53* and somatic *ATRX* mutations.

Group 2: Germline *TP53* mutations and no *ATRX* mutation

Group 3: Both wild-type *TP53* and *ATRX*.

DNA methylation studies further refined these classifications. Clay et al. identified two DNA methylation-based subgroups, pACT-1 and pACT-2, associated with clinical outcomes [18]. pACT-1 tumors, enriched for *CTNNB1* mutations, were associated with poor prognosis, while pACT-2 tumors, enriched for *TP53* germline variants, showed favorable outcomes and earlier onset. This contrasts with Pinto et al., where *TP53* germline alterations were associated with poorer survival [17]. These discrepancies may reflect differences in *TP53* variant types, patient age, or tumor biology. Notably, the CpG-island hypermethylator

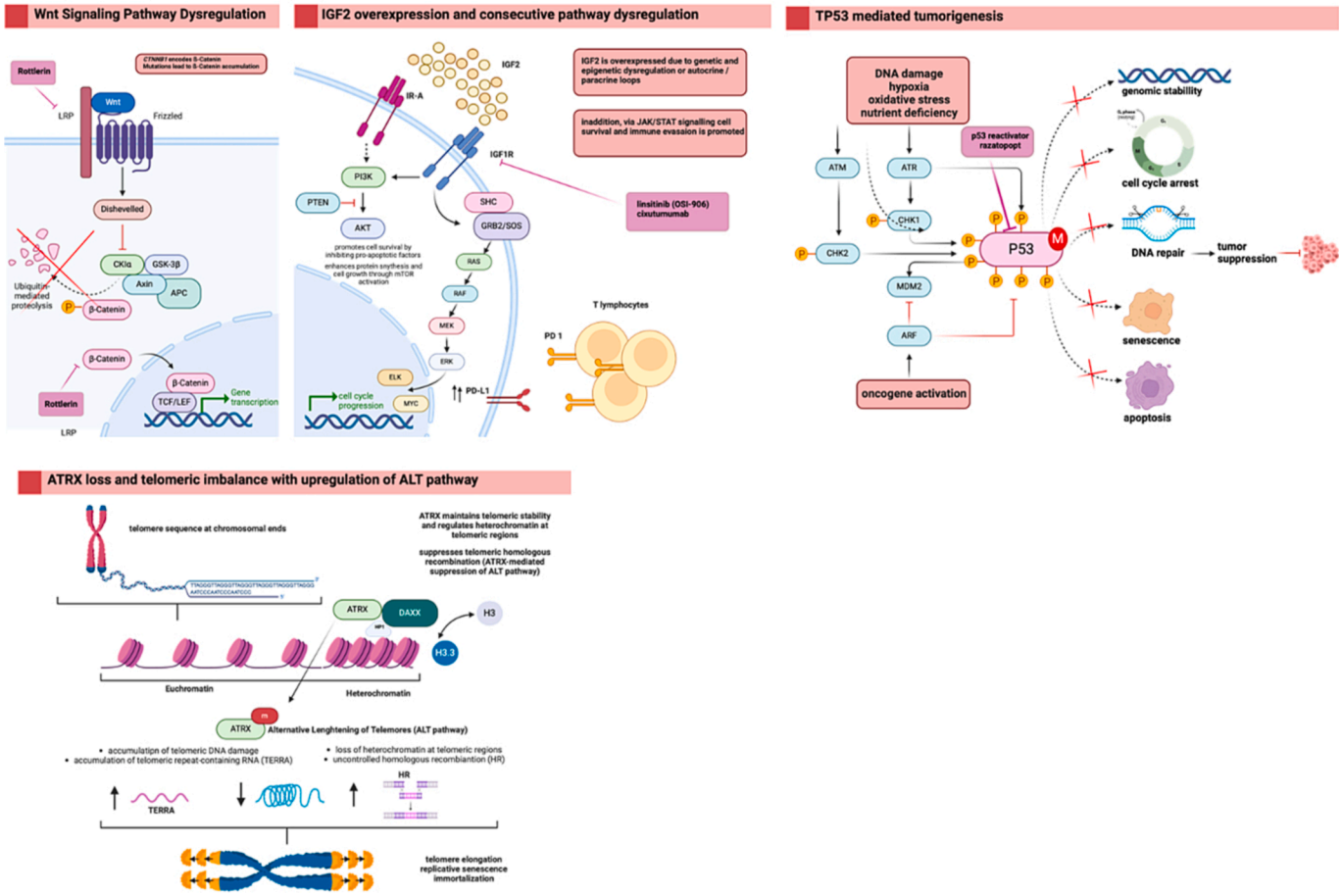

Fig. 1. Key signal transduction and repair pathways and therapeutic target structures in pediatric ACT.

phenotype observed in adult ACC was absent in pACT.

Expanding on these findings, recent methylation- and transcriptome-based analyses revealed four molecularly distinct subgroups [19,20]. A high-risk subgroup demonstrated significantly reduced 5-year overall survival (OS; 27 %) compared to 81 %-95 % in other subgroups. These tumors were diagnosed at higher ages and exhibited heightened proliferation programs.

Together, these molecular insights define the genetic underpinning of pACC and help guide efforts toward developing targeted therapies tailored to specific molecular subgroups.

Non-Coding RNA dysregulation

Non-coding RNAs (ncRNAs), including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), are increasingly recognized as critical regulators in the pathogenesis of pACT [21–23]. miRNAs, which post-transcriptionally regulate gene expression by targeting mRNA 3′ untranslated regions (UTRs), are implicated in oncogenesis and tumor suppression. While distinct miRNA expression patterns are well-characterized in adult ACC (reviewed in [18,19]), their role in pACC is now emerging, with significant implications for prognosis and therapeutic development.

Three pivotal studies have shed light on miRNA dysregulation in pACT. In the first, miR-149-3p was overexpressed in 67 pACT samples compared to non-neoplastic adrenal tissues. This miRNA was associated with unfavorable outcomes and promoted tumor cell viability, proliferation, and colony formation in vitro. Mechanistically, it down-regulated CDKN1A (p21), disrupting normal cell cycle control. These findings highlight miR-149-3p as a potential therapeutic target [21].

A second study identified miR-99a and miR-100 as regulators of the IGF-mammalian target of rapamycin(mTOR)-raptor signaling pathway in pACT. These miRNAs modulate mTOR signaling by binding 3′ UTRs of target genes, influencing tumor proliferation and survival. Inhibition of mTOR with everolimus reduced tumor growth in vitro and in vivo, underscoring the therapeutic relevance of targeting miRNA-mTOR interactions [22].

The third study profiled miRNA expression in 37 pACT samples and nine non-neoplastic tissues, identifying 98 differentially expressed miRNAs. A 17-miRNA signature strongly correlated with clinical outcomes, including relapse and mortality. Higher expression of hsa-miR-630, −139-3p, and −125a-3p, and lower levels of hsa-miR-377-3p, −126-3p, and −410, stratified patients into two prognostic groups with distinct 5-year event-free survival (EFS) rates. This signature was an independent prognostic factor, offering a robust biomarker for risk stratification [23].

lncRNAs, another major ncRNA class, function as epigenetic regulators, scaffolds, and decoys, modulating chromatin remodeling and gene expression. In adult ACC, specific lncRNAs such as ASB16-AS1 have been implicated in tumor suppression via promoting of HuR ubiquitination [24].

Other ncRNA classes, including piwi-interacting RNAs (piRNAs), small nuclear RNAs (snRNAs), and small nucleolar RNAs (snoRNAs), are also dysregulated in ACC and influence genomic stability and tumor suppressor pathways [25]. Although their role in pACC is less well defined, they likely contribute to the regulatory networks underlying tumorigenesis.

Collectively, these findings underscore the importance of ncRNA dysregulation, particularly miRNAs, in pACC biology. Emerging evidence supports their value in prognosis and therapy, with miR-149-3p and the 17-miRNA signature offer promising diagnostic and therapeutic avenues.

Cancer predisposition syndromes

pACC is frequently associated with cancer predisposition syndromes (CPS), highlighting a strong link between tumor development and hereditary genetic factors.

Li-Fraumeni syndrome (LFS)

LFS is caused by pathogenic variants in *TP53*, a key tumor suppressor involved in cell cycle regulation and apoptosis [26]. It is strongly associated with pACC, which represents the second most common malignancy in children with LFS, accounting for ~ 27 % of cases [27]. Notably, the *TP53* p.R337H (c.1010G > A, p.Arg337His) founder variant is highly prevalent in Brazilian populations, where 80–100 % of pACT cases are linked to LFS [28,29,30].

Beckwith-Wiedemann syndrome (BWS)

BWS is an overgrowth syndrome associated with epigenetic abnormalities of chromosome 11p15.5, including *IGF2* dysregulation. pACTs account for ~ 3 % of tumors in BWS and typically occur in early childhood [31–33].

Familial Adenomatous Polyposis (FAP)

FAP has also been associated with ACTs, including ACC [34,35]. *APC* mutations and subsequent activation of the Wnt/β-catenin pathway may contribute to adrenal tumorigenesis [34].

Other syndromes occasionally linked to pACTs include Multiple Endocrine Neoplasia type 1 (MEN1) [36,37] and Carney Complex (CNC) [38], though these associations are less well established.

Hormonal and metabolic Aspects

Steroid hormones and metabolomics are central to recent adult ACC research, reflecting the adrenal gland's pivotal role in steroid production. These hormones arise through steroidogenesis, a cascade converting cholesterol into cortisol, aldosterone, androgens, and estrogens [39]. In ACC, dysregulated steroidogenesis—marked by altered steroidogenic enzymes and receptors—not only drives tumor biology but also offers diagnostic and prognostic biomarker potential.

Plasma steroid hormone profiling

Plasma steroid hormone profiling shows promise as a diagnostic tool in adult ACC. In one LC-MS/MS-based study, 15 steroid hormones were measured in 66 ACA and 42 ACC patients [40]. ACC cases showed elevated levels of 11-deoxycorticosterone, progesterone, 17-hydroxyprogesterone, 11-deoxycortisol, DHEA, DHEAS, and estradiol. Logistic regression identified six steroids that improved diagnostic accuracy, with positive predictive values of 92 % in men and 96 % in women, and negative predictive values of 90 % and 86 %, respectively.

Serum steroid profiling has also been explored for monitoring disease progression and recurrence. In a cohort of 89 patients, markers like 11-deoxycortisol and testosterone detected "endocrine progress" before radiological evidence by a median of 32 days, underscoring the potential of LC-MS/MS for early disease detection [41].

Urine steroid hormone profiling

Urine steroid hormone profiling also shows utility in adult ACC. Several studies report significantly increased urinary excretion of androgen, mineralocorticoid, and glucocorticoid metabolites in ACC compared to ACA [42,43]. One study demonstrated that urinary profiling could distinguish malignant tumors in Cushing syndrome and adrenal neoplasms with over 90 % sensitivity and 100 % specificity [44]. Combining urinary profiling with imaging, (e.g., CT) and tumor diameter has enhanced diagnostic performance in evaluating adrenal incidentalomas [45].

A proof-of-concept study using GC–MS and machine learning detected recurrent ACC with 81 % sensitivity and specificity. Recurrent cases shared urinary profiles with their primary tumors, suggesting that preoperative profiling may aid in early recurrence detection [46].

Hormonal and metabolic insights in pediatric ACC

Data on steroid hormone metabolism in pACC remain limited, but recent GC–MS urinary steroid hormone profiling has yielded promising diagnostic insights. In one study, pACT patients showed elevated 5-ene-steroid metabolites (e.g., pregnenolone, 17-hydroxypregnenolone, DHEA) along with reduced activity of enzymes like 3β-hydroxysteroid dehydrogenase and 11-hydroxylase.

Importantly, GC–MS profiling distinguished pACCs from pACAs through metabolic signatures, including decreased corticosterone metabolites, increased 17-hydroxylase activity, and reduced 5α-reductase activity. These biomarkers achieved diagnostic accuracies exceeding 0.7 (ROC), supporting the potential of metabolic profiling as a non-invasive tool for pediatric ACC diagnosis [47]. Crucially, these metabolic profiles differ significantly from those observed in adult ACC, where distinct steroidogenic patterns and biomarker profiles have been reported.

A direct comparison between plasma and urinary steroid hormone profiling, as well as LC-MS/MS and GC–MS methodologies, remains largely unexplored in pACC. While LC-MS/MS-based plasma profiling is more accessible, its diagnostic performance relative to GC–MS urinary profiling in children is currently unknown. Standardizing steroid hormone profiling in pACC could substantially improve diagnosis, surveillance, and clinical management of pACC, enabling earlier detection, better risk stratification, and more personalized care.

Pediatric versus adult adrenocortical carcinoma

Pediatric and adult ACC exhibit distinct clinical, hormonal, genetic, and molecular characteristics, highlighting the need for age-specific management strategies. These differences influence not only presentation but also underlying biology and therapeutic approaches. (reviewed in [48,49]).

pACC typically shows significant endocrine activity, with symptoms such as virilization and Cushing syndrome commonly observed. In contrast, adult ACC often presents with non-functional tumors or isolated Cushing syndrome. Hormonal profiles in pACC are generally more pronounced, primarily driven by excess androgen production, whereas adult ACC exhibits a greater hormonal heterogeneity [8,50].

The genetic landscape of pACC also differs markedly. Pediatric cases are more frequently associated with inherited syndromes, most notably LFS, whereas adult ACC more often involves somatic mutations in genes such as *CTNNB1* and *ZNRF3*, reflecting alterations in the Wnt/β-catenin pathway. pACC also shows a higher prevalence of somatic chromosomal alterations and a distinct set of driver mutations [17,49].

In adult ACC, genomic profiling has identified actionable mutations in a subset of cases., approximately 10 % in unselected cohorts and up to 50 % in metastatic tumors. In contrast, only ~ 3 % of pACC cases harbor potentially actionable alterations, further underscoring the unique molecular landscape of pACC [49].

Prognosis is generally more favorable in pACC, likely due to differences in tumor biology and the greater effectiveness of surgical resection in younger patients [2,14,51–53]. Treatment approaches reflect these differences: surgery remains central to management in both groups, but in pACC, it is more commonly combined with chemotherapy [14,52,54–56]. Mitotane is more frequently used in adults [54,56,57]. Pediatric strategies prioritize balancing efficacy with long-term outcomes, while adult ACC often necessitates aggressive chemotherapy and is increasingly exploring targeted therapies [57–59].

While pACC and adult ACC share some overlapping features, their distinct genetic, hormonal, and clinical profiles necessitate tailored diagnostic and treatment approaches. Recognizing and addressing these differences is essential to improving outcomes and delivering age-appropriate care.

Current conventional therapeutic approaches in pACC

The clinical management of pACC follows a multimodal approach, combining surgical resection, chemotherapy, and mitotane therapy based on disease stage. The overarching goal is complete tumor removal and effective control of residual or metastatic disease.

The Children's Oncology Group (COG) classifies pACC into four stages according to disease extent and tumor characteristics (Table 1), guiding treatment and prognostic assessment [14].

Surgery

Surgical resection remains the cornerstone of localized pACC treatment. Adrenalectomy with R0 resection offers the best chance for long-term survival [2,3,11,13,14]. Michalkiewicz et al. reported a 5-year event-free survival (EFS) of 54 % with complete resection vs. 15 % with incomplete resection, a finding confirmed in subsequent studies [2,3,7,11–13]. Given the rarity and complexity of pACC, treatment at specialized pediatric oncology centers is recommended.

Chemotherapy

Chemotherapy is essential in advanced, residual, or metastatic disease, especially when initial resection is not feasible. Neoadjuvant chemotherapy may help downstage tumors and facilitate surgery [2,3,13–15]. The EDP regimen (etoposide, doxorubicin, cisplatin) plus mitotane is standard, though significant toxicity occurs in about one-third of patients [14]. Similar outcomes and toxicity have been reported with the alternating NN I/II regimen combined with mitotane [2,60].

Streptozotocin, in combination with mitotane, demonstrated efficacy in adult ACC in the FIRM-ACT trial [51]. However, its role in pACC remains undefined due to lack of pediatric-specific evidence.

Mitotane requires close monitoring due to its narrow therapeutic index and potential side effects, including adrenal insufficiency, gastrointestinal symptoms, and neurotoxicity [14,15,61].

The COG ARAR0332 trial stratified treatment by stage: Stage I patients fared well with surgery alone; stage III patients receiving EDP-mitotane had excellent outcomes; stage IV patients continued to have poor prognosis despite aggressive therapy [14]. However, stage II patients experienced high recurrence rates despite RPLND. This may reflect tumors with more aggressive biology, such as high Ki67 index, – not captured by conventional staging systems [57,62].

Radiation therapy

Radiation therapy is selectively used for local control in cases of incomplete resection, recurrence, or palliative treatment in metastatic disease [63,64]. Due to potential long-term side effects, especially in genetically predisposed children (e.g., LFS), its use is limited by the risk of secondary malignancies.

Challenges in treating pACC

pACC poses significant clinical challenges due to its aggressive behavior, high metastatic potential, and frequent relapse. Current treatment strategies often fall short, highlighting the urgent need for improved approaches informed by molecular insights.

Metastatic Disease: Obstacles and Limitations

Metastatic pACC progresses rapidly and most commonly spreads to the liver, lungs, and lymph nodes [2,14,63]. Management is difficult: complete surgical resection is rarely feasible, and debulking, while reducing tumor burden, is not curative and carries surgical risk [7]. Standard systemic therapies – mitotane, etoposide, doxorubicin, and

Table 1
Children's Oncology Group (COG) staging system for pediatric adrenocortical tumors and treatment recommendations.

COG stage	Definition	Treatment according to COG ARAR0332 protocol [14]	Treatment according to GPOH-MET 97 protocol [60]#	Therapeutic recommendations according to EXPeRT/ PARTNER [1]
Stage I	Completely resected, small tumors (<100 g and < 200 cm^3) with normal postoperative hormone levels.	Tumor resection	Stage I-III: T1-3, N0, M0 Tumor resection	Tumor resection
Stage II	Completely resected, large tumors (≥100 g and ≥ 200 cm^3) with normal postoperative hormone levels.	Tumor resection plus retroperitoneal lymph node dissection (RPLND)		Tumor resection Consider mitotane
Stage III	Unresectable tumors, presence of gross or microscopic residual disease, tumor spillage, patients with stage I and II tumors who do not achieve normal hormone levels postoperatively, or patients with nodal involvement	8 cycles of EDP chemotherapy Mitotane for 8 months, Tumor resection plus RPLND	Stage III: T1-2, N1, M0# Tumor resection 4 cycles of adjuvant NN I/ NN I chemotherapy Mitotane for 9 months	Tumor resection 6 cycles of (neo)adjuvant chemotherapy Mitotane for 1–2 years*
Stage IV	Presence of distant metastases.	8 cycles of EDP chemotherapy Mitotane for 8 months* Resection of primary tumor plus RPLND and of metastases as clinically indicated	Tumor resection and resection of metastases as clinically indicated 8 cycles of (neo)adjuvant NN I/NN I chemotherapy Mitotane for 18 months	Tumor resection and resection of metastases as clinically indicated 6–8 cycles of (neo)adjuvant chemotherapy (EDP or NN I/ NNII) Mitotane for 1–2 years*

according to American Joint Committee Cancer 7th edition.

cisplatin – achieve modest control, with median progression-free survival (PFS) of 5–9 months. Resistance frequently develops, limiting long-term efficacy [2,14,60,65].

Resistance mechanisms, such as genetic alterations and dysregulated signaling, remain poorly understood and present major barriers to progress [63]. Additionally, current imaging and biomarker tools fail to detect small metastases or early relapse, underscoring the need for better monitoring strategies.

High risk for relapse and refractory disease

Relapse and refractory disease are common, even after aggressive multimodal treatment [14,63]. Recurrence occurs in 37–50 % in stage II patients and exceeds 70 % in advanced stages (III and IV). Risk factors include positive margins, tumor spillage, large tumor size, and older age [2,3,13,14,66]. Management of refractory disease is complicated by rapid progression and resistance to conventional therapies.

Surgical re-resection can be critical for long-term survival in select relapsed cases [63]. Molecular drivers of resistance, such as alterations in the Wnt/β-catenin pathway, highlight the need for targeted strategies [9,18,19]. While imaging and hormone monitoring are standard, there is growing interest in circulating tumor DNA (ctDNA) as a more sensitive tool for early relapse detection.

Unmet needs and future Directions

The lack of standardized second-line treatment protocols in pACC often necessitates individualized treatment, made more challenging by limited first-line options. No validated biomarkers currently exist to guide therapy or predict outcomes. The scarcity of actionable molecular targets further limits development of precision therapies. Most available treatment data are derived from adult populations, creating uncertainty in pediatric care.

Moving forward, several priorities must be addressed: comprehensive molecular profiling to identify novel therapeutic targets; development of predictive biomarkers to guide individualized therapy; evaluation of targeted treatments aimed at key drivers of resistance and progression; and exploration of novel strategies including immunotherapies and rational drug combination. Crucially, more pediatric-specific data are needed to inform clinical decisions in this unique patient population.

In conclusion, overcoming the challenges of metastatic, relapsed, and refractory pACC will require a deeper understanding of its biology and the development of innovative, multimodal treatment strategies.

Preclinical models in pACC research

The development of targeted therapies for pACC is significantly hindered by the lack of robust preclinical models. In contrast to adult ACC, where human-derived cell lines and patient-derived xenografts (PDX) support translational research, pediatric equivalents are extremely limited or absent. The scarcity of pACC-specific cell lines and PDX models restricts functional studies of disease biology, evaluation of drug efficacy, and the translation of preclinical findings into clinical practice [67–70].

Advanced targeted therapies

Managing pACC remains challenging due to its aggressive nature and resistance to conventional therapies. Comprehensive genomic and multi-omics profiling is crucial to identify actionable mutations and tailor therapies that improve outcomes in high-risk cases [71,72].

This section reviews promising targeted therapies and the current state of research, most of which is derived from adult ACC patients.

Genomic and molecular targets

Targeting p53

TP53 encodes the tumor suppressor p53, a key regulator of cell cycle arrest, DNA repair, and apoptosis. Given the high frequency of both germline and somatic *TP53* mutations in pACC, [10,17] targeting p53 dysfunction represents a compelling therapeutic strategy. (Fig. 1).

Small molecules like PRIMA-1 and APR-246 (Eprenetapopt) aim to reactivate mutant p53 and induce apoptosis in cancer cell lines, though ACC-specific data remain limited [73,74].

MDM2 inhibitors prevent p53 by disrupting the p53-MDM2 interaction. Preclinical studies, including those in adult ACC, show promise with agents like Nutlin-3. Although no MDM2 inhibitors are currently approved, newer compounds, with orphan or fast-track designations, seek to improve potency, pharmacokinetics, and toxicity [75–77].

Given the central role of p53 in pACC, developing therapies that restore or stabilize p53 function, ideally in pediatric-specific trials, should be a priority. Combining MDM2 inhibitors or p53-restoring agents with chemotherapy or other targeted strategies may offer future treatment options.

Insulin-like growth factor (IGF) pathway inhibitors

The IGF2 pathway is essential for cell growth and development, and IGF2 overexpression is observed in nearly all pACC cases [17,78]. Targeting this axis offers significant therapeutic potential, though efficacy

in pediatric settings remains uncertain. (Fig. 1).

Current efforts focus on insulin-like growth factor 1 receptor (IGF1R) inhibitors, such as linsitinib (OSI-906), which block downstream tumor proliferation signals. IGF1R overexpression, linked to mTOR activation, correlates with relapse and metastasis in pACC [78,79]. In adult ACC cell lines, linsitinib reduced viability and induced apoptosis; combining IGF1R inhibitors with mitotane enhanced tumor suppression in vitro and in xenografts [78,80].

A phase I study of linsitinib showed tolerability with two adult ACC patients achieving partial responses at specific doses, though overall response rates were limited [81]. A subsequent phase III trial in metastatic ACC found no significant benefit over placebo [82]. Similarly, in a phase II trial of cixutumumab, a monoclonal IGF1R antibody, one of ten children with refractory pACC achieved stable disease [83].

Ongoing research is exploring predictive biomarkers and rational combination therapies, including co-targeting IGF1R and mTOR. The mTOR pathway integrates IGF signals and contains feedback loops linking mTORC1 and IGF signaling [84,85]. Importantly, given IGF1Rs role in normal growth and development, particularly in children, potential adverse effects on linear growth must be carefully monitored in clinical trials. Co-targeting IGF1R and mTOR may enhance efficacy and overcome resistance, but further research is needed to establish safety and effectiveness.

Developmental pathways in tumorigenesis

Wnt/β-Catenin pathway inhibitors

The Wnt/β-catenin pathway regulates cell proliferation, differentiation, and survival. Dysregulation is common in pACC and associated with high-risk disease [17,19]. Mutations in *CTNNB1*, which encodes β-catenin, are associated with aggressive tumor behavior and poor outcomes [17]. Targeting this pathway to restore normal signaling and inhibit tumor growth holds therapeutic potential [86,87] (Fig. 1).

Preclinical studies support this strategy. Rottlerin reduced proliferation, induced apoptosis, and caused G0/G1 arrest in adult ACC cell lines by downregulating LRP6 and β-catenin. In a nude mouse ACC model, it inhibited tumor growth and promoted apoptosis [88]. Abduch et al. found that YAP1, a downstream target of Wnt/β-catenin signaling, is overexpressed in pACT and correlates with poor prognosis, recurrence, and lower survival. Interestingly, inhibition of Wnt/β-catenin using PNU-74654, a Wnt/ß-catenin inhibitor, paradoxically increased YAP1 mRNA in adult ACC cell lines, suggesting compensatory mechanisms that may limit the efficacy of pathway inhibitors [89].

Despite its promise, clinical translation of Wnt pathway inhibitors remains challenging due to the pathway's complexity and vital physiological roles. Current approaches involve combining Wnt/β-catenin inhibitors with agents targeting parallel pathways (e.g., Hedgehog/GLI inhibitors) or using AI-driven drug screening to identify optimal combinations [90,91].

Hedgehog pathway inhibitors

The Hedgehog (Hh) signaling pathway is critical for embryogenesis and adrenal cortex development and remains active in both fetal and adult adrenal tissues. Its dysregulation has been observed in several cancers, including ACC. In pACTs, significantly reduced mRNA expression of SHH, PTCH1, SMO, GLI1, and GLI3 has been reported compared to normal pediatric adrenal tissue [92] (Fig. 2).

Preclinical studies suggest that inhibiting Hh signaling has antitumor potential. Cyclopamine reduced cell viability in adult ACC cell lines, while NVP-LDE225 (a Smoothened inhibitor) reduced tumor growth and hormone secretion in ACC models [92,93].

Though promising, pediatric-specific data remain scarce. FDA-approved Hh pathway inhibitors, such as vismodegib and sonidegib, are effective in basal cell carcinoma. However, in a phase I trial including two adult ACC patients, vismodegib did not produce any clinical responses [94].

In summary, while preclinical data support Hh pathway inhibition, its therapeutic role in ACC—especially pACC— remains unclear and warrants further study.

Notch pathway inhibitors

The Notch signaling pathway governs cell differentiation, proliferation, and apoptosis. Although widely implicated in cancer, effective clinical targeting remains limited. Emerging evidence suggests that antibody-drug conjugates (ADCs) targeting Notch ligands could be promising for ACC. (Fig. 2).

DLK1, a non-canonical Notch ligand, is overexpressed in adult ACC and represents a compelling target. Preclinical studies show that DLK1-directed ADCs like ADCT-701 exert potent cytotoxic effects in DLK1-positive ACC cell lines and patient-derived organoids by inducing DNA damage through receptor-mediated internalization [95].

Encouraged by these findings, a phase I trial (NCT06041516) is now evaluating ADCT-701 in adults with ACC and other tumor types, a step toward clinical translation [95].

Key challenges include confirming DLK1 specificity to avoid off-target toxicity and determing the feasibility of this approach in pACC.

Other Kinase pathways and enzymatic targets

Aurora Kinase inhibitors

Aurora kinases (AURKA and AURKB) regulate mitosis, including chromosome segregation and cytokinesis. Their dysregulation is implicated in various cancers, including ACC. Overexpression of AURKA/ B has been linked to poor prognosis in pACT, with higher expression correlating with reduced EFS and more aggressive phenotypes [96]. Targeting these kinases via Aurora kinase inhibitors (AKIs) may disrupt tumor cell proliferation and survival. (Fig. 2).

Preclinical studies have shown AKIs reduce proliferation and induce apoptosis in adult ACC models. AMG 900 increased apoptosis and enhanced chemosensitivity in the NCI-H295 cells [96,97]. Combined with PNU-74654 it produced greater tumor growth inhibition than

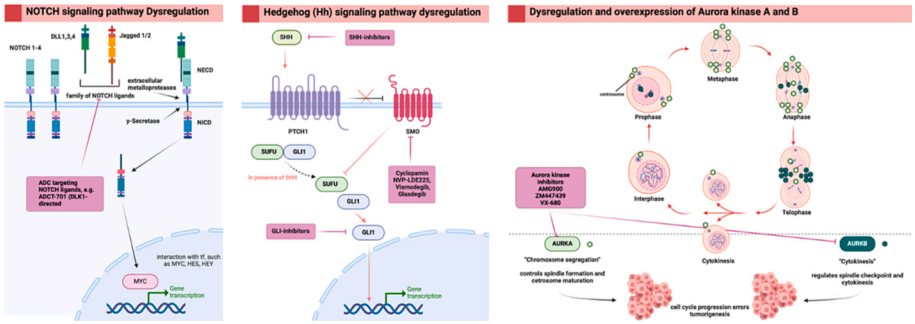

Fig. 2. Additional pathways contributing to pediatric ACT pathogenesis.

either agent alone [97].

The AKI ZM447439 inhibited proliferation in a childhood ACT culture with the *TP53* p.R337H mutation [96]. However, the AKI VX-680 showed limited efficacy in the H295R cells, emphasizing the need for model-specific approaches [98].

In summary, AKIs show promise in preclinical ACC models, but their clinical utility in pACC remains to be defined.

(Multi) Tyrosine Kinase inhibitors

Tyrosine kinases (TKIs), including receptor tyrosine kinases (RTKs), regulate proliferation, survival, migration, and angiogenesis. Sorafenib, targeting VEGFR, PDGFR, RET, and others, showed activity in adult ACC models, but residual disease limited long-term efficacy [99]. Similarly, the SIRAC trial of sunitinib showed modest results [100]. Notably, mitotane's CYP3A4 induction may reduce TKI efficacy and should be considered in treatment planning.

Combination strategies appear more effective. Sorafenib plus everolimus synergistically inhibited tumor growth and promoted apoptosis [101]. Cabozantinib (C-Met, VEGFR2, AXL, RET) achieved a 4-month PFS rate of 76 % and median OS of 24 months, though outcomes may be influenced by prior mitotane exposure [59].

TKIs paired with immune checkpoint inhibitors (ICIs) are also promising. Lenvatinib or cabozantinib plus pembrolizumab achieved a 58.8 % disease control rate and median PFS of 7.1 months in heavily pretreated adult ACC patients [58]. Although pediatric data are limited, a phase I study of cabozantinib in children with refractory solid tumors identified a safe dose of 40 mg/m^2/day, providing basis for future studies [102].

In conclusion, while single-agent TKIs show limited efficacy, rational combinations hold greater therapeutic potential.

MAPK/ERK pathway inhibitors

The MAPK/ERK (Mitogen-Activated Protein Kinase/Extracellular Signal-Regulated Kinase) pathway downstream of many RTKs regulates cell proliferation, differentiation, and survival. In adult ACC, ERK activation is frequently increased in malignant versus benign adrenal tissues [103].

Preclinical studies show that inhibitors such as PD184352 reduce proliferation and steroidogenesis in adult ACC cells, suggesting this pathway contributes to tumor growth and hormone production [103].

Despite its relevance in adult disease, studies on MAPK/ERK signaling and inhibition in pACC remain lacking.

Pi3K/AKT/mTOR pathway inhibitors

The PI3K/AKT/mTOR axis is central to survival and metabolic signaling and intersects with the IGF1R, MAPK/ERK and Wnt/β-catenin pathways. It plays a pivotal role in tumor progression and therapeutic resistance.

Dual PI3K/mTOR inhibitors such as PI-103 reduce proliferation and induce apoptosis in primary ACC cultures, including mitotane-resistant tumors [104]. PIK75, combined with HSP90 inhibitor STA9090, induced spheroid disintegration and apoptosis, suppressed PI3K targets (AKT, mTOR) and inhibited epithelial-mesenchymal transition, reducing metastatic potential [105].

While preclinical results are encouraging, clinical exploration in pACC is still absent.

Polo-like Kinase 1 (PLK1) inhibitors

PLK1 is essential for mitotic progression and is overexpressed in 30–60 % of adult ACC cases [106,107]. Inhibitors such as BI-2536 and rigosertib showed significant anti-tumor activity in *TP53*-mutant adult ACC cells and xenograft models [106,107].

However, clinical trials in pACC are currently lacking.

DNA metabolism and cell cycle control

Alterations in DNA repair and cell cycle regulators contribute to tumor progression and resistance. Targeting these mechanisms offers a promising strategy for precision medicine, particularly in tumors with defects in DNA damage response or checkpoint signaling.

PARP inhibitors

Poly(ADP-ribose) polymerase (PARP) inhibitors, such as rucaparib and olaparib, target enzymes involved in DNA repair via homologous recombination. Tumors with DNA repair deficiencies are particularly vulnerable, as PARP inhibition induces synthetic lethality in cancer cells.

In adult ACC, PARP inhibitors have shown mixed outcomes; for example, rucaparib showed limited efficacy in a patient with BRCA mutations post-chemotherapy [108]. However, in pediatric cancers, synthetic lethal interactions extent beyond BRCA alterations, indicating broader therapeutic potential [95]. A pediatric-specific synthetic lethal signature outperformed adult-derived signatures in predicting PARP inhibitor response across multiple pediatric tumor types [95],

Combining PARP inhibitors with standard chemotherapies also enhanced efficacy in preclinical pediatric cancer models. Moreover, ribosome biogenesis has been proposed as a predictive biomarker, potentially improving patient selection [109].

While data in pACC are lacking, the ability of PARP inhibitors to exploit DNA repair vulnerabilities makes them promising candidates. Further studies are needed to clarify their role and optimize their use in pACC.

Targeting the CDK4/6/Cyclin D/RB pathway

The CDK4/6/Cyclin D/RB axis regulates cell cycle progression. Cyclin-dependent kinases 4 and 6 (CDK4/6) complexes with Cyclin D to phosphorylate and inactivate the retinoblastoma (RB) protein, promoting from the G1-S phase transition. Dysregulation contributes to uncontrolled proliferation, and elevated CDK6 expression has been linked to poor prognosis in adult ACC [110].

CDK4/6 inhibitors, such as palbociclib and ribociclib, halt the cell cycle in G1, suppressing tumor growth. Preclinical studies in adult ACC cells have shown these agents reduce viability and induce senescence. Notably, palbociclib also induced apoptosis in RB-deficient ACC cells [110].

In the Pediatric MATCH trial, palbociclib was well tolerated in patients with solid tumors harboring CDK4/6 pathway alterations. However, no objective responses were observed, suggesting limited efficacy as monotherapy [111].

Combination strategies are being explored to improve outcomes. For example, CDK4/6 inhibitors combined with MEK inhibitors (e.g., trametinib) may enhance anti-tumor activity by co-targeting complementary pathways [112].

In conclusion, while CDK4/6 inhibitors offers a mechanistic rationale for targeting pACC and show promise in preclinical models, their standalone clinical activity appears limited.

Metabolic pathways

Targeting lipid metabolism and/or steroidogenesis

Lipid metabolism plays a critical role in tumor biology, affecting the tumor microenvironment, cancer progression, and therapeutic response. In adult ACC, transcriptomic studies have revealed alterations in genes involved in lipid and cholesterol metabolism. Upregulation of sphingolipid and steroid synthesis genes, such as *SGPL1*, *FDFT1*, and *SQLE*, correlates with poor survival, while *PIK3C2B* and *DGAT1*, involved in phosphatidylinositol and glycerol phospholipid metabolism, are downregulated [113]. These findings suggest that lipid metabolic reprogramming supports tumor progression and may offer exploitable vulnerabilities.

Sterol-O-acyl transferase 1 (SOAT1), also known as acyl-CoA acyltransferase 1 (ACAT1), catalyzes cholesterol esterification, a process essential for maintaining intracellular cholesterol homeostasis. SOAT1 has been implicated in tumor cell growth and survival, making it an appealing therapeutic target [114].

The SOAT1 inhibitor nevanimibe was evaluated in a phase I study in metastatic ACC. While no partial or complete responses were observed, some patients achieved stable disease. Notably, pharmacologic adrenal insufficiency occurred due to reduced steroidogenesis and apoptosis of adrenocortical cells [115]. These findings underscore the dual impact of SOAT1 inhibition on both lipid metabolic and steroid hormone production. Cholesterol plays a vital role in numerous cellular functions, including membrane integrity, signaling, and energy production. Thus, broader physiological effects of SOAT1 inhibition warrant careful evaluation.

In conclusion, targeting lipid metabolism represents a promising but still exploratory avenue in pACC therapy.

Steroidogenesis

Steroidogenesis, the enzymatic conversion of cholesterol into steroid hormones, is dysregulated in pACC and contributes to both tumor growth and clinical symptoms [8,47]. Key enzymes in this pathway include CYP11A1, CYP17A1, CYP21A2, and CYP11B1, which offer potential targets to reduce hormone excess and inhibit tumor progression.

Abiraterone acetate, a CYP17A1 inhibitor approved for prostate cancer, shows anti-secretory effects and has demonstrated potential in preclinical ACC studies [116]. Mitotane, the only FDA- and EMA-approved drug for ACC, controls hormone excess and prolongs recurrence-free survival in adults after radical resection. However, the ADIUVO trial showed limited benefit in low-risk patients [56,117].

In pACC, mitotane's role is less clearly defined; partial responses have been reported in about one-third of patients receiving neoadjuvant therapy [15].

Ketoconazole can rapidly normalize cortisol levels in adult ACC but does not significantly reduce tumor size; it may be combined with metyrapone to enhance inhibition of steroidogenesis [118–121].

Steroidogeneic factor-1 (SF-1), a transcription factor involved in steroidogenesis and cell proliferation, is often amplified in pACC, making it a potential therapeutic target [122,123]. SF-1 inverse agonists and combination strategies—including SOAT1 inhibitors or immune checkpoint inhibitors—may increase efficacy. Continued efforts to develop more selective and less toxic enzyme inhibitors and SF-1 modulators are essential to advance steroidogenesis-targeted therapies for pACC.

Immunotherapeutic approaches to pACC

Immunotherapy has revolutionized cancer treatment by mobilizing the immune system to recognize and attack tumor cells. Strategies that activate T-cells have shown potential in various malignancies.

Innovative immunotherapies

Immune checkpoint inhibitors (ICIs)

ICIs, such as pembrolizumab, avelumab, nivolumab, and ipilimumab, block checkpoint proteins (PD-1, PD-L1, and CTLA-4), used by cancer cells to evade immune surveillance. By inhibiting these checkpoints, ICIs restore T-cell-mediated tumor killing.

In adult ACC, response rates and PFS have been limited. (reviewed in [124]) Three biomarkers – PD-1 and PD-L1 expression, microsatellite instability (MSI), and tumor mutational burden (TMB) – may predict response and help guide patient selection.

Several ongoing trials are exploring ICIs as monotherapy or in combinations in adults. Pembrolizumab is being studied alone (NCT05563467) or with mitotane (NCT05634577) or lenvatinib (NCT05036434). Relacorilant, a glucocorticoid receptor modulator, is being tested with pembrolizumab to counter cortisol-mediated immunosuppression (NCT04373265). A terminated nivolumab trial reported modest activity (median PFS: 1.8 months; NCT02720484). A phase II trial is evaluating cabozantinib and atezolizumab (NCT06006013).

In pACC, data remain sparse. A phase 1–2 trial of pembrolizumab in pediatric patients with advanced melanoma or PD-L1-positive tumors showed partial responses in eight of 136 patients, including one with ACC [125]. While limited, these data emphasize the need for further investigation in pediatric settings. Hypersecretion of cortisol in ACC contributes to immune suppression and may hinder ICI's efficacy. Combination strategies, such as ICIs with multikinase inhibitors (e.g., lenvatinib, cabozantinib) or glucocorticoid receptor modulators (e.g., relacorilant) aim to enhance immune responsiveness.

Despite modest efficacy in adult ACC and limited pediatric data, ICIs remain a promising avenue. Expanding pediatric-specific trials, identifying predictive biomarkers, and evaluating combination regimens are key to optimizing their role in pACC.

CAR T-cell therapy

Chimeric Antigen Receptor (CAR) T-cell therapy uses genetically engineered T cells to specifically target tumor antigens. It has shown remarkable success in hematologic malignancies, and its application to solid tumors is under active exploration.

In pediatric ACC, B7-H3 has emerged as a promising target, expressed in over half of pACT. Preclinical studies with B7-H3-CAR T cells demonstrated potent antitumor effects. In PDX models of pACC, these cells achieved complete tumor eradication in some mice [126,127]. These results suggest CAR T-cell therapy could offer new hope for high-risk or chemotherapy-resistant pACC.

Challenges remain – off-tumor toxicity, immune suppression in the tumor microenvironment, and manufacturing scalability are significant barriers to clinical translation. Nonetheless, the strong preclinical foundation supports moving toward clinical trials of B7-H3-CAR T cells in pACC.

In conclusion, CAR T-cell therapy targeting B7-H3 presents a novel and highly promising approach for pACC. Continued preclinical work and well-designed clinical trials will be critical for realizing its therapeutic potential.

Epigenetic modifications in pACC

Epigenetic modifications, including DNA methylation and histone modifications, regulate gene expression without changing the underlying DNA sequence. In ACC, these modifications contribute to tumorigenesis by silencing tumor suppressor genes, activating oncogenes, and disrupting cell differentiation.

Recent studies have identified high-risk molecular subgroups in pACC characterized by aberrant CpG island methylation and WNT/β-catenin pathway activation, both associated with poor survival [19]. These findings underscore the potential of epigenetic therapies, particularly in tumors with extensive methylation-driven dysregulation.

DNA methylation inhibitors such as 5-azacytidine (azacitidine) and 5-aza-2′-deoxycytidine (decitabine) inhibit DNA methyltransferases, leading to DNA hypomethylation and reactivation of silenced genes. In preclinical adult ACC models, decitabine reduced tumor proliferation and enhanced the effects of standard chemotherapies such as doxorubicin, cisplatin, and etoposide [128,129]. However, epigenetic therapies in ACC remains an emerging field, with most evidence drawn from adult ACC models. Combining epigenetic agents with standard treatments or immunotherapies may improve efficacy by reactivating tumor suppressor genes or reshaping the immune microenvironment.

Radiopharmaceuticals

Radiopharmaceuticals offer a novel approach for diagnosing and treating ACC by targeting adrenal cortex-specific enzymes. These agents

provide both imaging and therapeutic potential, with promising results in adult patients. However, their application in pACC remains unexplored.

The novel CYP11B-ligand [(123/131)I]IMAZA has shown strong potential as a theranostic agent for ACCs by targeting CYP11B1 and CYP11B2, enabling enhanced specificity for adrenocortical tissue. Preclinical studies demonstrate greater metabolic stability compared to earlier compounds like [(123/131)I]iodometomidate (IMTO), which is rapidly inactivated. In vitro and in vivo experiments confirm high-affinity binding and selective accumulation in adrenocortical cells, allowing precise tumor targeting [130,131]. Early clinical data support improved imaging quality and pharmacokinetics with [(123/131)I]IMAZA over IMTO. In one case report, endoradiotherapy with [(131)I]IMAZA resulted in a progression-free interval of 21 months in an adult patient with advanced ACC [132].

Beyond CYP11B-targeted compounds, other radiopharmaceutical strategies are emerging. The C-X-C motif chemokine receptor 4 (CXCR4) has been identified as a promising target for both imaging and therapy, with potential for stratifying patients and refining therapeutic approaches [130,131]. Radiopharmaceuticals like [(123/131)I]IMAZA exemplify recent advancements in targeted diagnostics and treatment of ACC.

Although data are currently limited to adult cases, these findings pave the way for future investigation in pACC, particularly in high-risk or advanced settings.

Outlook and future Directions

pACCs present unique challenges due to its rarity, aggressiveness, and limited treatment options. Current strategies, largely adapted from adult protocols, rely on surgery, chemotherapy, and mitotane. However, the lack of robust pediatric-specific data and dedicated clinical trials underscores a critical gap in care and research.

Recent advances in molecular profiling have revealed actionable targets in signaling pathways (e.g., Wnt/β-catenin, MAPK/ERK), immune regulation, and epigenetics. Future therapies will likely combine these novel approaches with existing regimens, tailored to the unique biology of pACC.

Additionally, maintenance strategies and precise disease monitoring, such as steroid profiling and liquid biopsies, offer opportunities to enhance patient care.

Key Areas for progress

1. Clinical Trials and Novel Therapies: Early-phase clinical trials are essential to evaluate emerging treatments, particularly in metastatic, relapsed, or refractory pACC. Ensuring pediatric participation is critical to advancing knowledge and expanding access to innovative therapies.
2. International Collaboration and Data Sharing: Cooperative initiatives like the European Cooperative Study Group for Pediatric Rare Tumors (EXPeRT) and the proposed Pan-European pACT trial are pivotal for pooling expertise, resources, and patient data to drive progress in rare pediatric cancers.
3. Molecular Research and Targeted Therapies: Continued investigation into the molecular drivers of pACC, supported by improved preclinical models, will guide the development of combination regimens that integrate conventional therapies with targeted agents and immunotherapies.
4. Early Detection and Monitoring: Technologies such as liquid biopsy and comprehensive steroid hormone profiling enable earlier detection and dynamic monitoring, offering potential for timely interventions and individualized treatment adaptations.
5. Multidisciplinary and Comprehensive Care: A coordinated, multidisciplinary approach including oncologists, surgeons, geneticists, endocrinologists, and psychosocial experts is essential to provide holistic, long-term care for children with pACC.

Call to Action

Progress in pACC requires collaboration, innovation, and advocacy. Policymakers and funding agencies must prioritize rare cancer research, recognizing that underlying molecular mechanisms often transcend specific diagnoses. Expanding clinical trials to pediatric patients, investigating in biomarker development, and embracing precision oncology approaches, such as liquid biopsies and multi-omic profiling, will be key to advancing outcomes for this vulnerable population.

Conclusion

The fight against pACC reflects broader challenges in pediatric oncology: limited clinical data, unmet therapeutic needs, and the urgent necessity of collaborative research [16].

Grounding treatment in molecular insights, targeted therapies, and multidisciplinary care paves the way for personalized medicine in pediatric patients. Global initiatives, data sharing, and dedicated advocacy offer hope for better outcomes and brighter futures for affected children and their families.

Although progress has been made in adult ACC, these advances have yet to translate fully to pediatric cases. The distinct biological and clinical features of pACC demand specifically tailored strategies. Current therapies remain inadequate to meaningful improve long-term survival in children and adolescents with pACC.

Closing this gap requires intensified research, identification of novel targets, and development of innovative therapeutic approaches. By prioritizing pediatric-focused trials and fostering international collaboration, we can ensure that children with pACC benefit from in the full potential of modern oncology, delivering not just optimal care, but renewed hope for the future.

Funding

The research of MK on pACC is supported by Deutsche Kinderkrebsstiftung, grant number DKS 2021.11 and DKS 2024.16, Mitteldeutsche Kinderkrebsforschung, and Medical Faculty, University of Augsburg (intramurale Forschungsförderung).

Declaration of competing interest

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.

References

[1] Virgone C, Roganovic J, Vorwerk P, Redlich A, Schneider DT, Janic D, et al. Adrenocortical tumours in children and adolescents: The EXPeRT/PARTNER diagnostic and therapeutic recommendations. Pediatr Blood Cancer 2021;68 (Suppl 4):e29025.
[2] Kuhlen M, Kunstreich M, Wudy SA, Holterhus PM, Lessel L, Schneider DT, et al. Outcome for Pediatric Adreno-Cortical Tumors Is Best Predicted by the COG Stage and Five-Item Microscopic Score-Report from the German MET Studies. Cancers (Basel) 2022;15.
[3] Dall'Igna P, Virgone C, De Salvo GL, Bertorelle R, Indolfi P, De Paoli A, et al. Adrenocortical tumors in Italian children: analysis of clinical characteristics and P53 status. Data from the national registries. J Pediatr Surg 2014;49:1367–71.
[4] Siegel DA, King J, Tai E, Buchanan N, Ajani UA, Li J. Cancer incidence rates and trends among children and adolescents in the United States, 2001-2009. Pediatrics. 2014;134:e945-55.
[5] Rodriguez-Galindo C, Figueiredo BC, Zambetti GP, Ribeiro RC. Biology, clinical characteristics, and management of adrenocortical tumors in children. Pediatr Blood Cancer 2005;45:265–73.
[6] McAteer JP, Huaco JA, Gow KW. Predictors of survival in pediatric adrenocortical carcinoma: a Surveillance, Epidemiology, and End Results (SEER) program study. J Pediatr Surg 2013;48:1025–31.

[7] Michalkiewicz E, Sandrini R, Figueiredo B, Miranda EC, Caran E, Oliveira-Filho AG, et al. Clinical and outcome characteristics of children with adrenocortical tumors: a report from the International Pediatric Adrenocortical Tumor Registry. J Clin Oncol 2004;22:838–45.
[8] Kunstreich M, Dunstheimer D, Mier P, Holterhus PM, Wudy SA, Hubner A, et al. The endocrine phenotype induced by paediatric adrenocortical tumours is age- and sex-dependent. J Clin Endocrinol Metab 2024.
[9] Pinto EM, Rodriguez-Galindo C, Pounds SB, Wang L, Clay MR, Neale G, et al. Identification of Clinical and Biologic Correlates Associated With Outcome in Children With Adrenocortical Tumors Without Germline TP53 Mutations: A St Jude Adrenocortical Tumor Registry and Children's Oncology Group Study. J Clin Oncol 2017;35:3956–63.
[10] Wasserman JD, Novokmet A, Eichler-Jonsson C, Ribeiro RC, Rodriguez-Galindo C, Zambetti GP, et al. Prevalence and functional consequence of TP53 mutations in pediatric adrenocortical carcinoma: a children's oncology group study. J Clin Oncol 2015;33:602–9.
[11] Cecchetto G, Ganarin A, Bien E, Vorwerk P, Bisogno G, Godzinski J, et al. Outcome and prognostic factors in high-risk childhood adrenocortical carcinomas: A report from the European Cooperative Study Group on Pediatric Rare Tumors (EXPeRT). Pediatr Blood Cancer 2017;64.
[12] Zambaiti E, Duci M, De Corti F, Gamba P, Dall'Igna P, Ghidini F, et al. Clinical prognostic factors in pediatric adrenocortical tumors: A meta-analysis. Pediatr Blood Cancer 2021;68:e28836.
[13] Picard C, Faure-Conter C, Leblond P, Brugieres L, Thomas-Teinturier C, Hameury F, et al. Exploring heterogeneity of adrenal cortical tumors in children: The French pediatric rare tumor group (Fracture) experience. Pediatr Blood Cancer 2020;67:e28086.
[14] Rodriguez-Galindo C, Krailo MD, Pinto EM, Pashankar F, Weldon CB, Huang L, et al. Treatment of Pediatric Adrenocortical Carcinoma With Surgery, Retroperitoneal Lymph Node Dissection, and Chemotherapy: The Children's Oncology Group ARAR0332 Protocol. J Clin Oncol 2021;39:2463–73.
[15] Kuhlen M, Mier P, Kunstreich M, Lessel L, Schneider D, Brecht I, et al. Key factors for effective mitotane therapy in children with adrenocortical carcinoma. Endocr Relat Cancer 2022;29:545–55.
[16] Kuhlen M, Fruhwald MC. Bridging molecular advancements and clinical challenges in pediatric oncology. World J Pediatr 2024.
[17] Pinto EM, Chen X, Easton J, Finkelstein D, Liu Z, Pounds S, et al. Genomic landscape of paediatric adrenocortical tumours. Nat Commun 2015;6:6302.
[18] Clay MR, Pinto EM, Cline C, Tran QT, Lin T, Dyer MA, et al. DNA Methylation Profiling Reveals Prognostically Significant Groups in Pediatric Adrenocortical Tumors: A Report From the International Pediatric Adrenocortical Tumor Registry. JCO Precis. Oncol 2019;3.
[19] Fincke V, Loßner M, Sax I, Mucha M, Wudy S, Vokuhl C, et al. Investigating Single-Cell Transcriptomics to Navigate the Complexity of Pediatric Adrenocortical Tumors: Implications for Development, Prognosis, and Therapeutic Approaches. Pediatric Blood & Cancer. 2024;71:e31444; O271/#1814.
[20] Loßner M, Fincke V, Sax I, Mucha M, Wudy S, Vokuhl C, et al. Molecular Characterisation of Pediatric Adrenocortical Tumors Reveals Clinically Relevant Subgroups. Pediatric Blood & Cancer. 2024;71:e31444; O269/#1886.
[21] da Silva KR, Veronez LC, Correa CAP, Lira RCP, Baroni M, de Paula Silva Queiroz R,, et al. MicroRNA-149-3p expression correlates with outcomes of adrenocortical tumor patients and affects proliferation and cell cycle progression of H295A adrenocortical cancer cell line. Hum Cell 2022;35:1952–60.
[22] Doghman M, El Wakil A, Cardinaud B, Thomas E, Wang J, Zhao W, et al. Regulation of insulin-like growth factor-mammalian target of rapamycin signaling by microRNA in childhood adrenocortical tumors. Cancer Res 2010;70:4666–75.
[23] Veronez LC, Fedatto PF, Correa CAP, Lira RCP, Baroni M, da Silva KR, et al. MicroRNA expression profile predicts prognosis of pediatric adrenocortical tumors. Pediatr Blood Cancer 2022;69:e29553.
[24] Long B, Yang X, Xu X, Li X, Xu X, Zhang X, et al. Long noncoding RNA ASB16-AS1 inhibits adrenocortical carcinoma cell growth by promoting ubiquitination of RNA-binding protein HuR. Cell Death Dis 2020;11:995.
[25] Koduru SV, Leberfinger AN, Ravnic DJ. Small Non-coding RNA Abundance in Adrenocortical Carcinoma: A Footprint of a Rare Cancer. J Genomics 2017;5:99–118.
[26] Malkin D, Li FP, Strong LC, Fraumeni Jr JF, Nelson CE, Kim DH, et al. Germ line p53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms. Science 1990;250:1233–8.
[27] Bougeard G, Renaux-Petel M, Flaman JM, Charbonnier C, Fermey P, Belotti M, et al. Revisiting Li-Fraumeni Syndrome From TP53 Mutation Carriers. J Clin Oncol 2015;33:2345–52.
[28] Mai PL, Malkin D, Garber JE, Schiffman JD, Weitzel JN, Strong LC, et al. Li-Fraumeni syndrome: report of a clinical research workshop and creation of a research consortium. Cancer Genet 2012;205:479–87.
[29] Garritano S, Gemignani F, Palmero EI, Olivier M, Martel-Planche G, Le Calvez-Kelm F, et al. Detailed haplotype analysis at the TP53 locus in p.R337H mutation carriers in the population of Southern Brazil: evidence for a founder effect. Hum Mutat 2010;31:143–50.
[30] Achatz MI, Olivier M, Le Calvez F, Martel-Planche G, Lopes A, Rossi BM, et al. The TP53 mutation, R337H, is associated with Li-Fraumeni and Li-Fraumeni-like syndromes in Brazilian families. Cancer Lett 2007;245:96–102.
[31] Brioude F, Kalish JM, Mussa A, Foster AC, Bliek J, Ferrero GB, et al. Expert consensus document: Clinical and molecular diagnosis, screening and management of Beckwith-Wiedemann syndrome: an international consensus statement. Nat Rev Endocrinol 2018;14:229–49.
[32] Mussa A, Molinatto C, Baldassarre G, Riberi E, Russo S, Larizza L, et al. Cancer Risk in Beckwith-Wiedemann Syndrome: A Systematic Review and Meta-Analysis Outlining a Novel (Epi)Genotype Specific Histotype Targeted Screening Protocol. J Pediatr 2016;176(142–9):e1.
[33] Maas SM, Vansenne F, Kadouch DJ, Ibrahim A, Bliek J, Hopman S, et al. Phenotype, cancer risk, and surveillance in Beckwith-Wiedemann syndrome depending on molecular genetic subgroups. Am J Med Genet A 2016;170:2248–60.
[34] Gaujoux S, Pinson S, Gimenez-Roqueplo AP, Amar L, Ragazzon B, Launay P, et al. Inactivation of the APC gene is constant in adrenocortical tumors from patients with familial adenomatous polyposis but not frequent in sporadic adrenocortical cancers. Clin Cancer Res 2010;16:5133–41.
[35] Shiroky JS, Lerner-Ellis JP, Govindarajan A, Urbach DR, Devon KM. Characteristics of Adrenal Masses in Familial Adenomatous Polyposis. Dis Colon Rectum 2018;61:679–85.
[36] Pieterman CRC, van Leeuwaarde RS, van den Broek MFM, van Nesselrooij BPM, Valk GD. Multiple Endocrine Neoplasia Type 1. In: Feingold KR, Anawalt B, Blackman MR, Boyce A, Chrousos G, Corpas E, et al., editors. Endotext. South Dartmouth (MA)2000.
[37] Clemente-Gutierrez U, Pieterman CRC, Lui MS, Yamashita TS, Tame-Elorduy A, Huang BL, et al. Beyond the three P's: adrenal involvement in MEN1. Endocr Relat Cancer 2024;31.
[38] Stratakis CA, Kirschner LS, Carney JA. Clinical and molecular features of the Carney complex: diagnostic criteria and recommendations for patient evaluation. J Clin Endocrinol Metab 2001;86:4041–6.
[39] Wudy SA, Schuler G, Sanchez-Guijo A, Hartmann MF. The art of measuring steroids: Principles and practice of current hormonal steroid analysis. J Steroid Biochem Mol Biol 2018;179:88–103.
[40] Schweitzer S, Kunz M, Kurlbaum M, Vey J, Kendl S, Deutschbein T, et al. Plasma steroid metabolome profiling for the diagnosis of adrenocortical carcinoma. Eur J Endocrinol 2019;180:117–25.
[41] Kimpel O, Altieri B, Dischinger U, Fuss CT, Kurlbaum M, Fassnacht M. Early Detection of Recurrence and Progress Using Serum Steroid Profiling by LC-MS/MS in Patients with Adrenocortical Carcinoma. Metabolites 2023;14.
[42] Kikuchi E, Yanaihara H, Nakashima J, Homma K, Ohigashi T, Asakura H, et al. Urinary steroid profile in adrenocortical tumors. Biomed Pharmacother 2000;54(Suppl 1):194s–s197.
[43] Arlt W, Biehl M, Taylor AE, Hahner S, Libe R, Hughes BA, et al. Urine steroid metabolomics as a biomarker tool for detecting malignancy in adrenal tumors. J Clin Endocrinol Metab 2011;96:3775–84.
[44] Velikanova LI, Shafigullina ZR, Vorokhobina NV, Malevanaya EV. Gas Chromatography-Mass Spectrometry Analysis of Urinary Steroid Metabolomics for Detection of Early Signs of Adrenal Neoplasm Malignancy in Patients with Cushing's Syndrome. Bull Exp Biol Med 2019;167:676–80.
[45] Bancos I, Taylor AE, Chortis V, Sitch AJ, Jenkinson C, Davidge-Pitts CJ, et al. Urine steroid metabolomics for the differential diagnosis of adrenal incidentalomas in the EURINE-ACT study: a prospective test validation study. Lancet Diabetes Endocrinol 2020;8:773–81.
[46] Chortis V, Bancos I, Nijman T, Gilligan LC, Taylor AE, Ronchi CL, et al. Urine Steroid Metabolomics as a Novel Tool for Detection of Recurrent Adrenocortical Carcinoma. J Clin Endocrinol Metab 2020;105:e307–18.
[47] Hartmann M, Pons-Kühnemann J, Kunstreich M, Redlich A, Vorwerk P, Kuhlen M, et al. Detection and differentiation of adrenocortical tumors (ACTs) in children by gas chromatography- mass spectrometry (GC-MS) based urinary steroid metabotyping. Hormone Research in Paediatrics. 2024;97:1-736, Abstr FC8.2.
[48] Faria AM, Almeida MQ. Differences in the molecular mechanisms of adrenocortical tumorigenesis between children and adults. Mol Cell Endocrinol 2012;351:52–7.
[49] Crona J, Beuschlein F. Adrenocortical carcinoma - towards genomics guided clinical care. Nat Rev Endocrinol 2019;15:548–60.
[50] Chukkalore D, MacDougall K, Master V, Bilen MA, Nazha B. Adrenocortical Carcinomas: Molecular Pathogenesis, Treatment Options, and Emerging Immunotherapy and Targeted Therapy Approaches. Oncologist 2024;29:738–46.
[51] Fassnacht M, Terzolo M, Allolio B, Baudin E, Haak H, Berruti A, et al. Combination chemotherapy in advanced adrenocortical carcinoma. N Engl J Med 2012;366:2189–97.
[52] O'Neill AF, Ribeiro RC, Pinto EM, Clay MR, Zambetti GP, Orr BA, et al. Pediatric Adrenocortical Carcinoma: The Nuts and Bolts of Diagnosis and Treatment and Avenues for Future Discovery. Cancer Manag Res 2024;16:1141–53.
[53] Hescot S, Debien V, Hadoux J, Drui D, Haissaguerre M, de la Fouchardiere C, et al. Outcome of adrenocortical carcinoma patients included in early phase clinical trials: Results from the French network ENDOCAN-COMETE. Eur J Cancer 2023;189:112917.
[54] Fassnacht M, Dekkers OM, Else T, Baudin E, Berruti A, de Krijger R, et al. European Society of Endocrinology Clinical Practice Guidelines on the management of adrenocortical carcinoma in adults, in collaboration with the European Network for the Study of Adrenal Tumors. Eur J Endocrinol 2018;179:G1–46.
[55] Riedmeier M, Decarolis B, Haubitz I, Muller S, Uttinger K, Borner K, et al. Adrenocortical Carcinoma in Childhood: A Systematic Review. Cancers (Basel) 2021;13.
[56] Terzolo M, Fassnacht M, Perotti P, Libe R, Kastelan D, Lacroix A, et al. Adjuvant mitotane versus surveillance in low-grade, localised adrenocortical carcinoma

(ADIUVO): an international, multicentre, open-label, randomised, phase 3 trial and observational study. Lancet Diabetes Endocrinol 2023;11:720–30.
[57] Grisanti S, Cosentini D, Lagana M, Turla A, Berruti A. Different management of adrenocortical carcinoma in children compared to adults: is it time to share guidelines? Endocrine 2021;74:475–7.
[58] Yaylaci Mert F, Balderrama Brondani V, Marcal LP, Campbell M, Jimenez C, Varghese J, et al. 7959 Combination Therapy Of Multi-Targeted Tyrosine Kinase Inhibitors And Immune Checkpoint Inhibitors In Advanced Adrenocortical Carcinoma. J Endocr Soc 2024;8.
[59] Campbell MT, Balderrama-Brondani V, Jimenez C, Tamsen G, Marcal LP, Varghese J, et al. Cabozantinib monotherapy for advanced adrenocortical carcinoma: a single-arm, phase 2 trial. Lancet Oncol 2024;25:649–57.
[60] Redlich A, Boxberger N, Strugala D, Fruhwald MC, Leuschner I, Kropf S, et al. Systemic treatment of adrenocortical carcinoma in children: data from the German GPOH-MET 97 trial. Klin Padiatr 2012;224:366–71.
[61] Riedmeier M, Antonini SRR, Brandalise S, Costa T, Daiggi CM, de Figueiredo BC, et al. International consensus on mitotane treatment in pediatric patients with adrenal cortical tumors: Indications, therapy, and management of adverse effects. Eur J Endocrinol 2024.
[62] Wieneke JA, Thompson LD, Heffess CS. Adrenal cortical neoplasms in the pediatric population: a clinicopathologic and immunophenotypic analysis of 83 patients. Am J Surg Pathol 2003;27:867–81.
[63] Kuhlen M, Kunstreich M, Lessel L, Wudy SA, Holterhus P-M, Vokuhl C, et al. Refractory and relapsed paediatric ACC in the MET studies – A challenging situation necessitating novel diagnostic and therapeutic concepts. EJC Paediatric. Oncology 2023;1.
[64] Wiegering V, Riedmeier M, Thompson LDR, Virgone C, Redlich A, Kuhlen M, et al. Radiotherapy for pediatric adrenocortical carcinoma - Review of the literature. Clin Transl Radiat Oncol 2022;35:56–63.
[65] Kuhlen MS, C; Fuchs, J; Kunstreich, M; Johann, P; Claus, R; Frühwald, M; Vorwerk, P; Redlich, A. Oligo- and polymetastatic paediatric adrenocortical carcinoma – distinct conditions necessitating different treatment approaches? Presented at European Congress of Endocrinology 2024, Stockholm, Sweden. Presented at Society for Endocrinology 2024, Stockholm, Sweden. Endocrine Abstracts. 2024; Volume 99:EP557.
[66] Kuhlen M, Mier P, Kunstreich M, Lessel L, Slavetinsky C, Fuchs J, et al. Locally Advanced Adrenocortical Carcinoma in Children and Adolescents—Enigmatic and Challenging Cases. Cancers 2023;15:4296.
[67] Sedlack AJH, Hatfield SJ, Kumar S, Arakawa Y, Roper N, Sun NY, et al. Preclinical Models of Adrenocortical Cancer. Cancers (Basel) 2023;15.
[68] Pinto EM, Kiseljak-Vassiliades K, Hantel C. Contemporary preclinical human models of adrenocortical carcinoma. Curr Opin Endocr Metab Res 2019;8:139–44.
[69] Wang T, Rainey WE. Human adrenocortical carcinoma cell lines. Mol Cell Endocrinol 2012;351:58–65.
[70] Sigala S, Bothou C, Penton D, Abate A, Peitzsch M, Cosentini D, et al. A Comprehensive Investigation of Steroidogenic Signaling in Classical and New Experimental Cell Models of Adrenocortical Carcinoma. Cells 2022;11.
[71] Lippert J, Appenzeller S, Liang R, Sbiera S, Kircher S, Altieri B, et al. Targeted Molecular Analysis in Adrenocortical Carcinomas: A Strategy Toward Improved Personalized Prognostication. J Clin Endocrinol Metab 2018;103:4511–23.
[72] Hescheler DA, Hartmann MJM, Riemann B, Michel M, Bruns CJ, Alakus H, et al. Targeted Therapy for Adrenocortical Carcinoma: A Genomic-Based Search for Available and Emerging Options. Cancers (Basel) 2022;14.
[73] Duffy MJ, Synnott NC, Crown J. Mutant p53 as a target for cancer treatment. Eur J Cancer 2017;83:258–65.
[74] Perdrix A, Najem A, Saussez S, Awada A, Journe F, Ghanem G, et al. PRIMA-1 and PRIMA-1(Met) (APR-246): From Mutant/Wild Type p53 Reactivation to Unexpected Mechanisms Underlying Their Potent Anti-Tumor Effect in Combinatorial Therapies. Cancers (Basel) 2017;9.
[75] Twarda-Clapa A. An update patent review of MDM2-p53 interaction inhibitors (2019-2023). Expert Opin Ther Pat 2024.
[76] Wang W, Albadari N, Du Y, Fowler JF, Sang HT, Xian W, et al. MDM2 Inhibitors for Cancer Therapy: The Past, Present, and Future. Pharmacol Rev 2024;76:414–53.
[77] Yao Y, Zhang Q, Li Z, Zhang H. MDM2: current research status and prospects of tumor treatment. Cancer Cell Int 2024;24:170.
[78] Peixoto Lira RC, Fedatto PF, Marco Antonio DS, Leal LF, Martinelli CE, de Castro M, et al. IGF2 and IGF1R in pediatric adrenocortical tumors: roles in metastasis and steroidogenesis. Endocr Relat Cancer 2016;23:481–93.
[79] Almeida MQ, Fragoso MC, Lotfi CF, Santos MG, Nishi MY, Costa MH, et al. Expression of insulin-like growth factor-II and its receptor in pediatric and adult adrenocortical tumors. J Clin Endocrinol Metab 2008;93:3524–31.
[80] Barlaskar FM, Spalding AC, Heaton JH, Kuick R, Kim AC, Thomas DG, et al. Preclinical targeting of the type I insulin-like growth factor receptor in adrenocortical carcinoma. J Clin Endocrinol Metab 2009;94:204–12.
[81] Jones RL, Kim ES, Nava-Parada P, Alam S, Johnson FM, Stephens AW, et al. Phase I study of intermittent oral dosing of the insulin-like growth factor-1 and insulin receptors inhibitor OSI-906 in patients with advanced solid tumors. Clin Cancer Res 2015;21:693–700.
[82] Fassnacht M, Berruti A, Baudin E, Demeure MJ, Gilbert J, Haak H, et al. Linsitinib (OSI-906) versus placebo for patients with locally advanced or metastatic adrenocortical carcinoma: a double-blind, randomised, phase 3 study. Lancet Oncol 2015;16:426–35.
[83] Weigel B, Malempati S, Reid JM, Voss SD, Cho SY, Chen HX, et al. Phase 2 trial of cixutumumab in children, adolescents, and young adults with refractory solid tumors: a report from the Children's Oncology Group. Pediatr Blood Cancer 2014;61:452–6.
[84] Houghton P. Targeting the IGF-1/mTOR pathway. Clinical Cancer Research. 2014;14:PL05-3-PL-3.
[85] Ardestani A, Maedler K. mTORC1 and IRS1: Another Deadly Kiss. Trends Endocrinol Metab 2018;29:737–9.
[86] Krishnamurthy N, Kurzrock R. Targeting the Wnt/beta-catenin pathway in cancer: Update on effectors and inhibitors. Cancer Treat Rev 2018;62:50–60.
[87] Low JL, Du W, Gocha T, Oguz G, Zhang X, Chen MW, et al. Molecular docking-aided identification of small molecule inhibitors targeting beta-catenin-TCF4 interaction. iScience 2021;24:102544.
[88] Zhu Y, Wang M, Zhao X, Zhang L, Wu Y, Wang B, et al. Rottlerin as a novel chemotherapy agent for adrenocortical carcinoma. Oncotarget 2017;8:22825–34.
[89] Abduch RH, Carolina Bueno A, Leal LF, Cavalcanti MM, Gomes DC, Brandalise SR, et al. Unraveling the expression of the oncogene YAP1, a Wnt/beta-catenin target, in adrenocortical tumors and its association with poor outcome in pediatric patients. Oncotarget 2016;7:84634–44.
[90] de Pellegars-Malhortie A, Picque Lasorsa L, Mazard T, Granier F, Prevostel C. Why Is Wnt/beta-Catenin Not Yet Targeted in Routine Cancer Care? Pharmaceuticals (Basel) 2024;17.
[91] Goyal A, Murkute SL, Bhowmik S, Prasad CP, Mohapatra P. Belling the "cat": Wnt/beta-catenin signaling and its significance in future cancer therapies. Biochim Biophys Acta Rev Cancer 2024;1879:189195.
[92] Gomes DC, Leal LF, Mermejo LM, Scrideli CA, Martinelli Jr CE, Fragoso MC, et al. Sonic hedgehog signaling is active in human adrenal cortex development and deregulated in adrenocortical tumors. J Clin Endocrinol Metab 2014;99:E1209–16.
[93] Camponova P, Bezine M, Duparc C, Cao CD, Aubert S, Lefebvre H, et al. Sonic Hedgehog signaling pathway is expressed in normal human adrenal cortices and up-regulated in adrenocortical carcinomas. Ann Endocrinol 2022;83:322.
[94] LoRusso PM, Rudin CM, Reddy JC, Tibes R, Weiss GJ, Borad MJ, et al. Phase I trial of hedgehog pathway inhibitor vismodegib (GDC-0449) in patients with refractory, locally advanced or metastatic solid tumors. Clin Cancer Res 2011;17:2502–11.
[95] Sun N-Y, Kumar S, Weiner A, Kim YS, Mendoza A, Nguyen R, et al. Targeting DLK1, a Notch ligand, with an antibody-drug conjugate in adrenocortical carcinoma [abstract]. Proceedings of the American Association for Cancer Research Annual Meeting 2024; Part 1. 2024;84.
[96] Borges KS, Moreno DA, Martinelli Jr CE, Antonini SR, de Castro M, Tucci Jr S, et al. Spindle assembly checkpoint gene expression in childhood adrenocortical tumors (ACT): Overexpression of Aurora kinases A and B is associated with a poor prognosis. Pediatr Blood Cancer 2013;60:1809–16.
[97] Maria AG, Silva Borges K, Lira RCP, Hassib Thome C, Berthon A, Drougat L, et al. Inhibition of Aurora kinase A activity enhances the antitumor response of beta-catenin blockade in human adrenocortical cancer cells. Mol Cell Endocrinol 2021;528:111243.
[98] Pezzani R, Rubin B, Bertazza L, Redaelli M, Barollo S, Monticelli H, et al. The aurora kinase inhibitor VX-680 shows anti-cancer effects in primary metastatic cells and the SW13 cell line. Invest New Drugs 2016;34:531–40.
[99] Cerquetti L, Bucci B, Raffa S, Amendola D, Maggio R, Lardo P, et al. Effects of Sorafenib, a Tyrosin Kinase Inhibitor, on Adrenocortical Cancer. Front Endocrinol (Lausanne) 2021;12:667798.
[100] Kroiss M, Quinkler M, Johanssen S, van Erp NP, Lankheet N, Pollinger A, et al. Sunitinib in refractory adrenocortical carcinoma: a phase II, single-arm, open-label trial. J Clin Endocrinol Metab 2012;97:3495–503.
[101] Araujo AN, Bugalho MJ. Advanced Adrenocortical Carcinoma: Current Perspectives on Medical Treatment. Horm Metab Res 2021;53:285–92.
[102] Chuk MK, Widemann BC, Minard CG, Liu X, Kim A, Bernhardt MB, et al. A phase 1 study of cabozantinib in children and adolescents with recurrent or refractory solid tumors, including CNS tumors: Trial ADVL1211, a report from the Children's Oncology Group. Pediatr Blood Cancer 2018;65:e27077.
[103] Pereira SS, Monteiro MP, Costa MM, Ferreira J, Alves MG, Oliveira PF, et al. MAPK/ERK pathway inhibition is a promising treatment target for adrenocortical tumors. J Cell Biochem 2019;120:894–906.
[104] Zhang J, Wu L, Su T, Liu H, Jiang L, Jiang Y, et al. Pharmacogenomic analysis in adrenocortical carcinoma reveals genetic features associated with mitotane sensitivity and potential therapeutics. Front Endocrinol (Lausanne) 2024;15:1365321.
[105] Mishra P, Shen M, Hall M, Zhang Y-Q, Nilubol N. RF07 | PSUN356 Synergistic Combination of HSP90 and PI3K inhibitors in Adrenocortical Cancer. Journal of the Endocrine Society. 2022;6:A895-A.
[106] Bussey KJ, Bapat A, Linnehan C, Wandoloski M, Dastrup E, Rogers E, et al. Targeting polo-like kinase 1, a regulator of p53, in the treatment of adrenocortical carcinoma. Clin Transl Med 2016;5:1.
[107] Warmington E, Smith G, Chortis V, Liang R, Lippert J, Steinhauer S, et al. PLK1 inhibitors as a new targeted treatment for adrenocortical carcinoma. Endocr. Connect 2024;13.
[108] Greb AC, Reikes AR. Efficacy of Treatment With PARP Inhibitor and Immunotherapy for Aggressive Adrenocortical Carcinomawith Cushing's Syndrome Refractory to Treatment With EDP Chemotherapy and Mitotane. J Endocr Soc 2021;5:A129–30.
[109] Keller KM, Koetsier J, Schild L, Amo-Addae V, Eising S, van den Handel K, et al. The potential of PARP as a therapeutic target across pediatric solid malignancies. BMC Cancer 2023;23:310.
[110] Hadjadj D, Kim SJ, Denecker T, Ben Driss L, Cadoret JC, Maric C, et al. A hypothesis-driven approach identifies CDK4 and CDK6 inhibitors as candidate

drugs for treatments of adrenocortical carcinomas. Aging (Albany NY) 2017;9:2695–716.
[111] Macy ME, Mody R, Reid JM, Piao J, Saguilig L, Alonzo TA, et al. Palbociclib in solid tumor patients with genomic alterations in the cyclin D-CDK4/6-INK4a-Rb pathway: Results from NCI-COG pediatric MATCH trial Arm I (APEC1621I). Journal of Clinical Oncology. 2023;41:10006-.
[112] Wu J, Wang J, O'Connor TN, Tzetzo SL, Gurova KV, Knudsen ES, et al. Separable Cell Cycle Arrest and Immune Response Elicited through Pharmacological CDK4/6 and MEK Inhibition in RASmut Disease Models. Mol Cancer Ther 2024;23:1801–14.
[113] Subramanian C, Cohen MS. Identification of novel lipid metabolic biomarkers associated with poor adrenocortical carcinoma prognosis using integrated bioinformatics. Surgery 2022;171:119–29.
[114] Tu T, Zhang H, Xu H. Targeting sterol-O-acyltransferase 1 to disrupt cholesterol metabolism for cancer therapy. Front Oncol 2023;13:1197502.
[115] Smith DC, Kroiss M, Kebebew E, Habra MA, Chugh R, Schneider BJ, et al. A phase 1 study of nevanimibe HCl, a novel adrenal-specific sterol O-acyltransferase 1 (SOAT1) inhibitor, in adrenocortical carcinoma. Invest New Drugs 2020;38:1421–9.
[116] Fiorentini C, Fragni M, Perego P, Vezzoli S, Bonini SA, Tortoreto M, et al. Antisecretive and Antitumor Activity of Abiraterone Acetate in Human Adrenocortical Cancer: A Preclinical Study. J Clin Endocrinol Metab 2016;101:4594–602.
[117] Terzolo M, Angeli A, Fassnacht M, Daffara F, Tauchmanova L, Conton PA, et al. Adjuvant mitotane treatment for adrenocortical carcinoma. N Engl J Med 2007;356:2372–80.
[118] Harinarayan CV, Gupta S, Ammini AC, Karmarkar MG, Gupta R, Sharma LK, et al. Clinical utility of ketoconazole in cases of adrenocortical carcinoma. Indian J Cancer 1991;28:196–201.
[119] Verhelst JA, Druwe P, van Erps P, Denis LJ, Mahler C. Use of ketoconazole in the treatment of a virilizing adrenocortical carcinoma. Acta Endocrinol (Copenh) 1989;121:229–34.
[120] Corcuff JB, Young J, Masquefa-Giraud P, Chanson P, Baudin E, Tabarin A. Rapid control of severe neoplastic hypercortisolism with metyrapone and ketoconazole. Eur J Endocrinol 2015;172:473–81.
[121] Neto LS, Filho AG, Bustorff-Silva JM, Koler H, Epelman S, Marini SH, et al. Preoperative control of arterial hypertension using ketoconazole in pediatric patients with adrenocortical tumors. J Pediatr Endocrinol Metab 2000;13:201–4.
[122] Relav L, Doghman-Bouguerra M, Ruggiero C, Muzzi JCD, Figueiredo BC, Lalli E. Steroidogenic Factor 1, a Goldilocks Transcription Factor from Adrenocortical Organogenesis to Malignancy. Int J Mol Sci 2023;24.
[123] Doghman M, Lalli E. A matter of dosage: SF-1 in adrenocortical development and cancer. Ann Endocrinol (Paris) 2009;70:148–52.
[124] Araujo-Castro M, Pascual-Corrales E, Molina-Cerrillo J, Alonso-Gordoa T. Immunotherapy in Adrenocortical Carcinoma: Predictors of Response, Efficacy, Safety, and Mechanisms of Resistance. Biomedicines 2021;9.
[125] Geoerger B, Kang HJ, Yalon-Oren M, Marshall LV, Vezina C, Pappo A, et al. Pembrolizumab in paediatric patients with advanced melanoma or a PD-L1-positive, advanced, relapsed, or refractory solid tumour or lymphoma (KEYNOTE-051): interim analysis of an open-label, single-arm, phase 1-2 trial. Lancet Oncol 2020;21:121–33.
[126] Pinto EM, R. E, Santiago T, Sheppard HS, Clay MR, Morton CL, et al. Abstract: 12485: Evaluating B7-H3-CAR T Cell Therapy In Preclinical Models Of Pediatric Adrenocortical Tumors. J Endocr Soc 2024;8.
[127] R. E, Pinto EM, SaRebecca T, Epperly E, Pinto M, Santiago T, et al. Abstract 1197: B7-H3-CAR T cells for the treatment of pediatric adrenocortical carcinoma. Cancer Research. 2023;83:1197-.
[128] Gao ZH, Suppola S, Liu J, Heikkila P, Janne J, Voutilainen R. Association of H19 promoter methylation with the expression of H19 and IGF-II genes in adrenocortical tumors. J Clin Endocrinol Metab 2002;87:1170–6.
[129] Suh I, Weng J, Fernandez-Ranvier G, Shen WT, Duh QY, Clark OH, et al. Antineoplastic effects of decitabine, an inhibitor of DNA promoter methylation, in adrenocortical carcinoma cells. Arch Surg 2010;145:226–32.
[130] Michalski K, Schlotelburg W, Hartrampf PE, Kosmala A, Buck AK, Hahner S, et al. Radiopharmaceuticals for Treatment of Adrenocortical Carcinoma. Pharmaceuticals (Basel) 2023;17.
[131] Werner RA, Hartrampf PE, Schirbel A, Hahner S. Adrenal functional imaging - which marker for which indication? Curr Opin Urol 2022;32:585–93.
[132] Heinze B, Schirbel A, Nannen L, Michelmann D, Hartrampf PE, Bluemel C, et al. Novel CYP11B-ligand [(123/131)I]IMAZA as promising theranostic tool for adrenocortical tumors: comprehensive preclinical characterization and first clinical experience. Eur J Nucl Med Mol Imaging 2021;49:301–10.