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Evolving Precision Therapy Paradigm against Adrenocortical Carcinoma

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Abstract

Adrenocortical carcinoma (ACC) is a rare and highly aggressive endocrine cancer type, posing significant clinical challenges due to its diverse molecular features and poor treatment outcomes. At the molecular level, abnormalities in pathways, such as IGF2 signaling, Wnt/β-catenin activation, cell-cycle regulation, DNA damage repair, chromatin remodeling, and steroidogenesis have been implicated in ACC biology. The complex tumor microenvironment, marked by immune exclusion, angiogenic activity, and cortisol-driven immunosuppression, contributes to tumor progression and therapy resistance. A growing shift toward more precise and mechanism-based therapeutic strategies has led to the advent of several targeted approaches, such as IGF-1R and mTOR inhibition, VEGFR- and multi-kinase-directed therapies, and Wnt and cell-cycle modulators. These approaches have shown promising preclinical anti-tumor activity, though clinical benefit remains variable. Immunotherapy has also emerged as an important frontier in the treatment of ACC, with PD-1/PD-L1 inhibitors, dual checkpoint blockade, combination treatments with VEGFR tyrosine kinase inhibitor and immune checkpoint inhibitor, and glucocorticoid receptor modulation showing encouraging results, especially in patients with microsatellite instability-high tumors. Furthermore, next-generation therapeutic platforms, including radiopharmaceuticals, antibody-drug conjugates, neoantigen-based vaccines, engineered cellular therapies, nanotechnology-based delivery systems, and AI-driven biomarker and drug discovery, are novel avenues being explored in the field ACCs. Collectively, this review explores these insights contributing to the evolving precision therapy paradigm that has the potential to reshape the therapeutic management of ACC and provide more individualized options for patients in the future.

Key words adrenocortical carcinoma, targeted therapy, tyrosine kinase inhibitors, immunotherapy, antibody-drug conjugates, cancer vaccine

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Introduction

Adrenocortical carcinoma (ACC) is a rare and aggressive endocrine malignancy with an annual incidence of 0.7 to 2 cases per million worldwide. Despite its low prevalence, ACC has been associated with remarkably high morbidity and mortality [1, 2]. Although 5-year survival generally approaches 60-80% in localized disease, most patient subsets exhibit poor prognosis as outcomes sharply decline to 35-50% in locally advanced ACC and to less than 30% in metastatic disease scenarios [3, 4]. The only potentially curative option is complete surgical resection. Even among these patients, recurrence rates remain alarmingly high, affecting up to 70% of individuals with stage I-III disease, thereby resulting in a median disease-free survival of just 11 months [5]. Population-based datasets also show similar trends, and consistently document high relapse rates and a median overall survival (OS) of just around 14 months for patients with unresectable or metastatic disease [6, 7].

Mitotane, an adrenolytic agent, along with cytotoxic chemotherapy has historically dominated the therapeutic landscape for ACC. Although the FIRM-ACT trial has established the combination of etoposide, doxorubicin, and cisplatin with mitotane (EDP-M) as key first-line systemic therapy, it only yields a 23% objective response rate, with 5 and 14.8 months of median progression-free survival (PFS) and median OS respectively [8]. Other cytotoxic regimens have demonstrated only little to no benefit and are typically used for subsequent lines of therapy or for patients unable to tolerate EDP-M [9]. Mitotane therapy has its own limitations including, but not limited to, delayed achievement of therapeutic plasma concentrations, variable pharmacokinetics driven by CYP3A4 induction, and significant gastrointestinal and neurologic toxicity [10, 11]. Overall, better-tolerated, and more effective therapeutic strategies need to be developed to tackle ACC.

Advances in genomics and multi-omics profiling during the last decade have transformed our understanding of ACC biology. Three major molecular subtypes (COC1-COC3) have been established, each with distinctive genomic, transcriptomic, and epigenetic features, with markedly unique clinical outcomes [12]. Recurring alterations in different oncogenic pathways leading to IGF2 overexpression, Wnt/β-catenin dysregulation through CTNNB1 or ZNRF3 mutations, disruption of cell-cycle and p53-dependent apoptotic control, chromatin remodeling defects, and aberrations in DNA damage repair mechanisms have been found to be associated with tumorigenesis in ACC [4, 6]. Aberrations in tumor microenvironment, marked by immune exclusion and angiogenic remodeling, further aid in the tumor heterogeneity and therapeutic resistance in ACCs [13, 14]. Therefore, integrating molecular profiling into clinical decision-making is suggested to identify actionable vulnerabilities, which will improve patient stratification, and refine the deployment of targeted therapies, immunotherapies, and combination strategies [15, 16]. This approach is potentially critical for rare cancers including ACC, where limited patient numbers, conventional trial designs, and heterogeneous treatment responses mask the therapeutic innovation.

In this review, we explore genomic, epigenomic, and microenvironmental insights into ACC biology, and present rapidly evolving precision-therapy landscape against this cancer. In addition, we discuss ongoing advancements in targeted agents, immunotherapy, radiopharmaceuticals and next-generation precision modalities, all of which have the potential to delineate a promising framework for personalized treatment of ACC, highlighting a future with translational opportunities reshaping the clinical outcomes in ACC patients.

Genomic architecture and molecular pathogenesis of ACC

ACCs are marked by genetic alterations, chromatin remodeling, metabolic reprogramming, tumor microenvironment aberrations and the interactions between these factors. With the help of mutli-omics analyses, biological subgroups of ACC with distinct vulnerabilities and clinical profiles have been established during the last decade [12]. Three principal ACC molecular subtypes, COC1, COC2, and COC3, exhibit unique genomic, transcriptomic, and epigenetic signatures, associated with distinct clinical trajectories and outcomes [12]. Among these subtypes, COC1 is marked by low proliferative potential, reduced copy-number alterations, and favorable outcomes; whereas COC2 harbors intermediate genomic instability; while COC3 is noted for chromosomal aberrations including gains and losses, increased methylation burden, and the worst survival. Notably, the CpG island methylator phenotype (CIMP) has been found to be strongly enriched in aggressive tumors, and correlates with genomic instability and inferior prognosis in ACC patients [12, 17]. Although tumor mutational burden is not that pronounced in ACC compared to several other malignancies, patient clusters characterized by mismatch repair defects, including those associated with Lynch syndrome have been identified [12].

In the context of oncogenic signaling pathways, the IGF2/IGF1R signaling axis represents one of the most consistently dysregulated pathways in ACC, with IGF2 overexpression occurring in up to 90% of tumors [13]. IGF2 hyperactivation is attributed to aberrant imprinting at chromosome 11p15. This event promotes mitogenic and anti-apoptotic signaling via activation of PI3K/AKT/mTOR and RAS/RAF/MEK/ERK axes, leading to cell-cycle progression, metabolic adaptation, and survival of cancer cells in ACCs [13, 18]. Aberrant activation of the Wnt/β-catenin pathway due to somatic mutations in CTNNB1, primarily affecting exon 3 phosphorylation sites, leads to β-catenin stabilization and nuclear accumulation. This drives transcription of genes involved in proliferation, invasion, and cellular dedifferentiation [12, 17]. Loss-of-function of ZNRF3, a negative regulator of Wnt signaling leads to uncontrolled pathway activation, correlating with aggressive disease [19, 20]. Disruption of cell-cycle checkpoints, such as mutations in TP53 tumor suppressor are frequently observed in both sporadic tumors and those associated with Li-Fraumeni syndrome. These events compromise DNA damage responses, and promote genomic instability and resistance to apoptosis. Concomitantly, alterations in CDKN2A, RB1, CDK4, and CCNE1 deregulate G1/S transition, fostering unchecked proliferation [13, 21]. Alterations in mismatch repair, homologous recombination repair, and DNA damage responses regulators, such as ATR, ATM, and CHEK2, are evident in ACCs. These events contribute to genomic instability, mutational load, and therapeutic resistance [3, 17]. Mismatch repair deficiency associates ACC with Lynch syndrome. ACC tumors with microsatellite instability-high (MSI-H) are rare (~3%), but these tumors demonstrate enhanced responsiveness to immune checkpoint inhibition [22]. Mutations in epigenetic factors TERT, ATRX, and DAXX are associated with disrupted telomere maintenance, leading to replicative immortality and facilitating chromosomal instability [23, 24]. Promoter hypermethylation and CIMP-high states lead to inhibition of tumor suppressor genes and modulation of steroidogenic pathways, resulting in poor-prognosis of COC3 subtype. Therefore, targeting epigenetic regulators, such as HDAC and DNMT, is a key therapeutic frontier in ACC as well [25, 26]. Aberrant activation of cAMP-PKA signaling through PRKAR1A loss or pathway dysregulation also contributes to abnormal steroidogenesis and accelerated proliferation of cancer cells in ACCs [27, 28]. Overall, all these signaling axes intertwine with intrinsic oncogenic pathways (**Figure 1**), amplifying tumor aggressiveness and complicating therapeutic intervention.

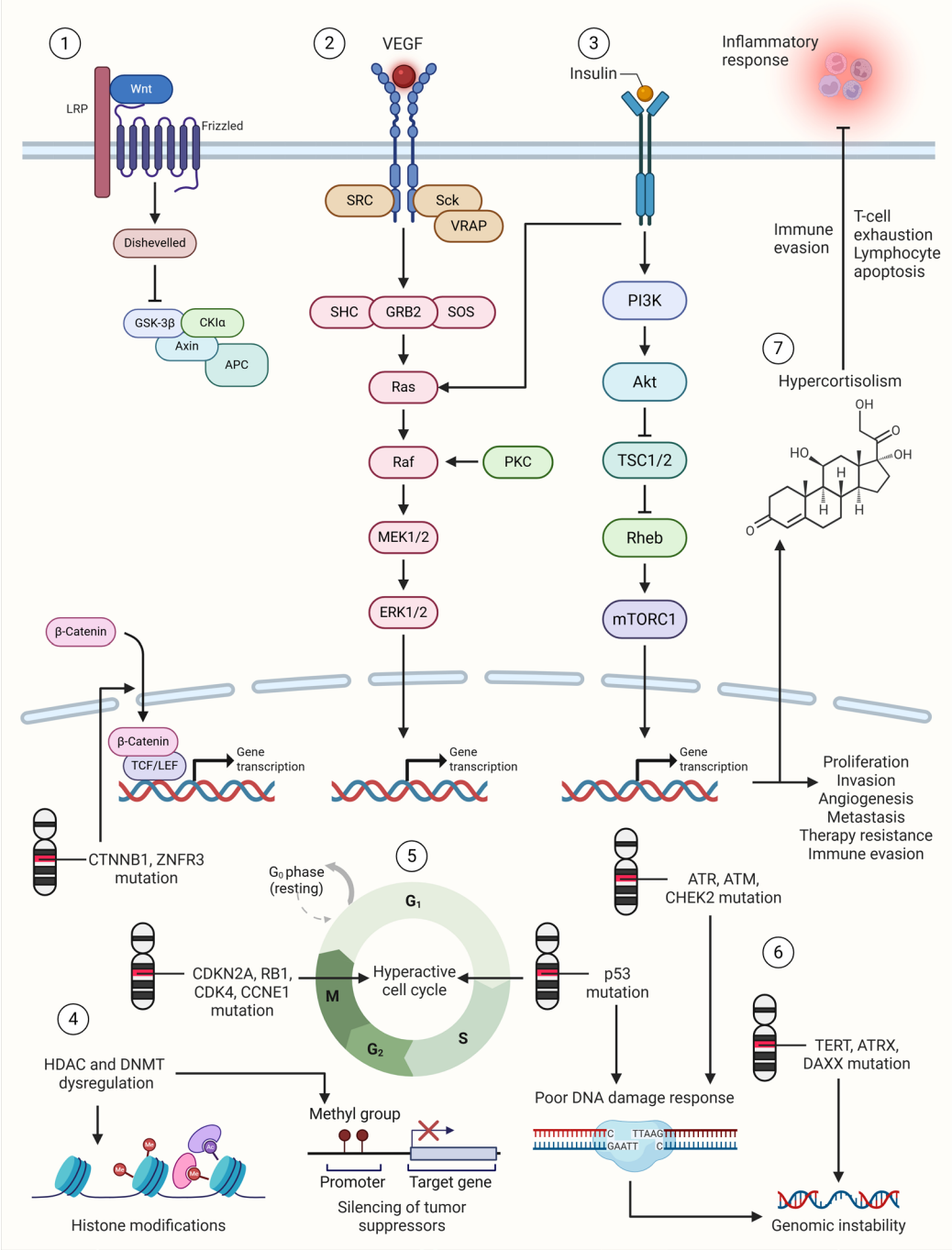

Figure 1. Genomic and molecular landscape of adrenocortical carcinoma. 1) Aberrant activation of Wnt signaling through mutations in CTNNB1 and loss of ZNRF3, leads to β-catenin stabilization, nuclear accumulation, and transcription of genes involved in cell proliferation and invasion. 2) VEGF signaling promotes endothelial cell proliferation and angiogenesis, essential for tumor growth, nutrient supply, and metastasis. 3) IGF2 overexpression activates mitogenic and anti-apoptotic signaling through the PI3K/AKT/mTOR and RAS/RAF/MEK/ERK axes, driving tumor cell survival and proliferation. 4) Modifications in histones and DNA methylation and acetylation patterns due to HDAC and DNMT dysregulation contribute to silencing of tumor suppressor genes in aggressive ACC subtypes. 5) Mutations in key cell-cycle regulators (e.g., CDKN2A, RB1, CDK4, CCNE1) and DNA damage repair genes (e.g., TP53) compromise cell-cycle checkpoints, contributing to hyperactive cell cycle and tumor progression. 6) Mutations in DNA damage repair genes (e.g., TP53, ATM, ATR, CHEK2) lead to poor DNA damage response, which along with mutations in TERT, ATRX and DAXX results in genomic instability. 7) Hypercortisolism in ACC promotes immune evasion by inducing T-cell exhaustion and lymphocyte apoptosis, further complicating therapeutic efficacy.

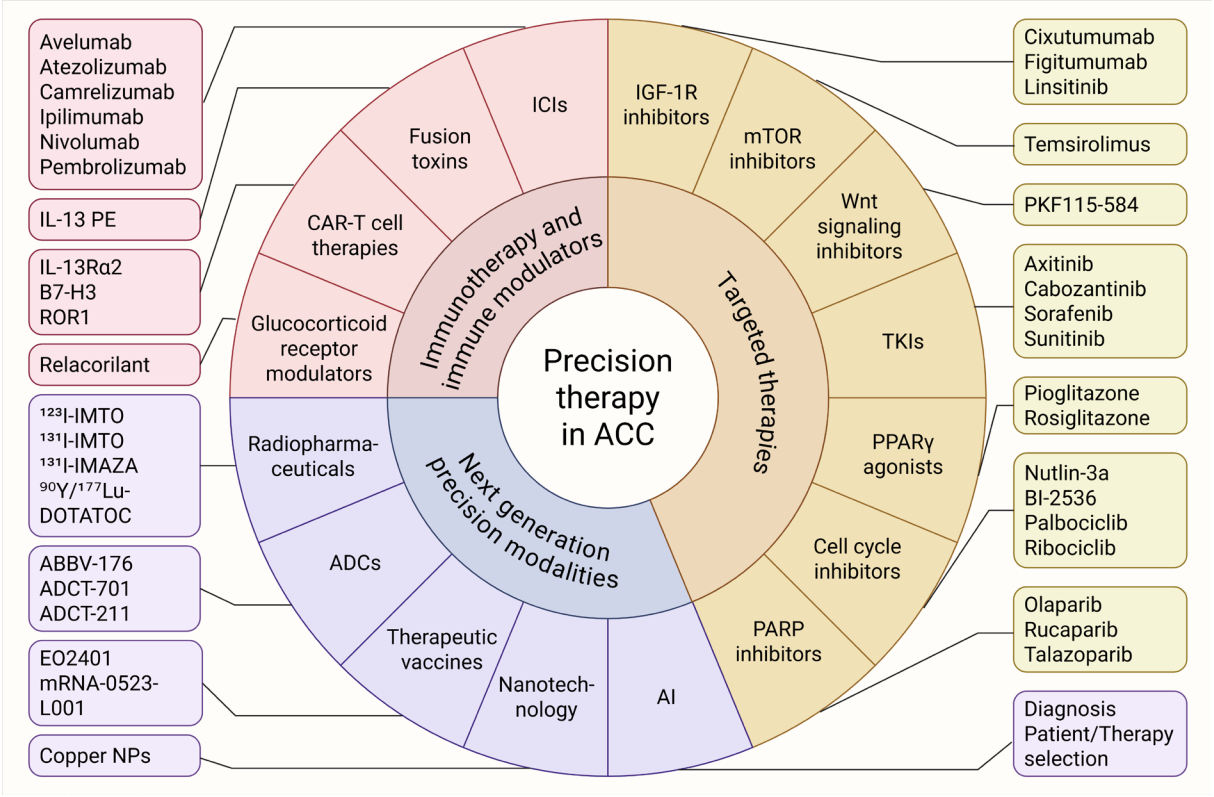

Figure 2. Evolving precision-guided therapeutics in ACC. Targeted therapies (IGF-1R inhibitors, mTOR inhibitors, Wnt signaling inhibitors, TKIs, cell-cycle inhibitors, and PARP inhibitors), immunotherapy and immune modulators (ICIs along with their combination strategies, fusion toxins, CAR-T therapies, and glucocorticoid receptor modulators) and next-generation precision modalities (radiopharmaceuticals, ADCs, therapeutic vaccines, nanotechnology and AI) represent key approaches for personalized therapy against ACC. AI: Artificial intelligence, ADC: Antibody-drug conjugate, ICI: Immune checkpoint inhibitor, NP: Nanoparticle, TKI: Tyrosine kinase inhibitor.

Tumor microenvironment and immune evasion in ACC

Tumor microenvironment in ACC is highly specialized and profoundly immunosuppressive. It is often marked by an immune-excluded or immune-desert phenotype, having low levels of effector T-cell infiltration, poor antigen presentation, and suppressed pro-inflammatory signaling. It has also been demonstrated by multi-omics studies that ACC generally harbors low tumor mutational burden as compared to other solid tumors. This factor eventually limits the production of immunogenic neoantigens within the tumor microenvironment as required for robust T-cell priming [29, 30]. Although alterations in DNA damage response or mismatch repair pathways do exist frequently in ACC, similar to all other cancer types, only a small number of ACCs show MSI-H status. This factor also predominantly supports the non-immunogenic nature of the disease [31]. The presence of hypercortisolism is also a proof of ACC-associated immune suppression, a phenomenon observed in almost half of all the metastatic ACC tumors [30, 32]. This excess of cortisol is responsible for significant immunosuppressive activity via lymphocyte apoptosis, T-cell exhaustion, and inhibition of antigen-presentation [33, 34]. Suppressed cytotoxic T-cell recruitment and poor responsiveness to immune checkpoint blockade, particularly in microsatellite-stable tumors, is also attributed to this cortisol-driven immunologic impairment. It has been noted that immune checkpoint inhibitors (ICIs) retain partial efficacy in some cortisol-secreting ACCs, as reported by retrospecttive and prospective analyses, but their response rates are often lower than cortisol-independent disease [35-37].

Angiogenic program driven by VEGF, FGF2, and other pro-vasculogenic cytokines in the tumor microenvironment also promotes tumor progression in ACC, leading to endothelial proliferation, improved nutrient availability, and enhanced vascular permeability [21, 38]. Advanced stage ACC also shows increased serum levels of VEGF and high VEGFR expression on the surface of tumor cells. This indirectly suggests that angiogenic signaling plays key roles in tumor maintenance and survival in ACC [39, 40]. On the other hand, vasculogenic mimicry is also a key feature of ACCs, where vessel-like structures independent of endothelial cells are formed, thereby providing an additional survival edge to the tumors, other than conventional angiogenic pathways [39]. This alternative vascular channel formation capacity also helps metastatic spread of the disease, support growth under hypoxic conditions, and promote resistance against VEGF-targeted therapies, as demonstrated by clinical trials of first-generation VEGFR tyrosine kinase inhibitors (TKIs), such as sorafenib, sunitinib, and axitinib in ACCs [38, 41]. Tumor microenvironment also has cancer-associated fibroblasts, extracellular matrix, and stromal signaling molecular networks which promote tumor proliferation and invasion. Most notably, TGF-β1 is secreted by both tumor cells and stromal elements, and aids in developing a pro-invasive phenotype by promoting epithelial-to-mesenchymal transition, and by limiting immune effector cell activation [30]. Overall, tumor microenvironment in ACC is a complex,

Table 1. Therapeutic trials in adrenocortical carcinoma with targeted and immunotherapies.

Trial	Drugs	Mechanism of action	Phase	Primary outcomes	Status
NCT00453895 (SIRAC)	Sunitinib	VEGFR TKI	II	ORR, PFS (primary)	Terminated
NCT01255137	Axitinib	VEGFR TKI	II	ORR (primary), OS, DCR, PFS, safety (secondary)	Terminated
NCT02637531 (MARIO-1)	Nivolumab + IPI-549 (Eganelisib)	ICI + PI3K inhibitor	I	DLT, ORR, DOR, PFS, OS, IPI-549 plasma concentrations	Active, not recruiting
NCT02720484	Nivolumab	ICI (single-agent)	II	ORR (primary), PFS, OS, Safety (secondary)	Terminated
NCT02721732	Pembrolizumab	ICI (single-agent)	II	NPR (primary), ORR, PFS, Safety (secondary)	Active, not recruiting
NCT02867592	Cabozantinib	VEGFR TKI	II	ORR (primary), Safety, Tissue-banking (secondary)	Active, not recruiting
NCT03333616	Nivolumab + Ipilimumab	ICI (dual)	II	ORR (primary), DOR, PFS, OS, Safety (secondary)	Terminated
NCT03370718	Cabozantinib	VEGFR TKI	II	PFS4 (primary), ORR, PFS, OS, Safety (secondary)	Terminated
NCT03612232 (CaboACC)	Cabozantinib	VEGFR TKI	II	PFS4 (primary), ORR, PFS, OS, Safety (secondary)	Active, not recruiting
NCT04187404 (SPENCER)	Nivolumab + EO2401	ICI + Vaccine	I/II	Safety (primary), PFS, OS, Immuno-genicity (secondary)	Terminated
NCT04318730	Apatinib + Camrelizumab	VEGFR TKI + ICI	II	ORR (primary), OS, DCR, PFS, safety (secondary)	Recruiting
NCT04400474 (CABATEN/ GETNE-T1914)	Cabozantinib + Atezolizumab	VEGFR TKI + ICI	II	ORR (primary), PFS, OS, Safety (secondary)	Terminated
NCT05036434 (ACCOMPLISH)	Lenvatinib + Pembrolizumab	VEGFR TKI + ICI	II	ORR (primary), DCR	Enrolling by invitation
NCT05634577	Pembrolizumab + Mitotane	ICI + Steroidogenesis Inhibitor	II	ORR (primary)	Terminated
NCT06006013	Cabozantinib + Pembrolizumab	VEGFR TKI + ICI	II	ORR (primary), PFS, OS, Safety (secondary)	Active, not recruiting
NCT06066333	Pembrolizumab + Radiotherapy	ICI + Radiotherapy	II	Safety (primary)	Active, recruiting
SAT−175 Trial	Cabozantinib	VEGFR TKI	II	PFS (primary), ORR, OS, Safety (secondary)	Terminated

DCR: Disease control rate, DLT: Dose-limiting toxicity, DOR: Duration of response, ICI: Immune checkpoint inhibitor, ORR: Objective response rate, OS: Overall survival, PFS: Progression-free survival, TKI: Tyrosine kinase inhibitor.

multilayered hurdle against therapeutic success.

Evolving precision-guided therapeutics in ACC

The transition from empiric cytotoxic therapy toward precision-guided systemic strategies represents a pivotal shift in the therapeutic landscape of ACC. In this section, we will discuss the key progress in the areas of targeted therapies against oncogenic signaling pathways, immunotherapy and immune modulators, and next-generation precision modalities (**Figure 2**).

Targeted therapies against oncogenic signaling pathways

The IGF pathway has long been regarded as one of the most actionable oncogenic drivers in ACC due to the near-universal overexpression of IGF2 and its downstream activation of IGF-1R-mediated proliferative cascades [13]. Early preclinical studies demonstrated potent anti-tumor effects with IGF1R inhibition, including growth suppression and apoptotic induction in ACC cell lines, particularly when combined with mitotane [42]. Figitumumab and cixutumumab are key monoclonal antibodies targeting IGF-1R. Treatment with these monoclonal antibodies in ACC has shown good tolerability in early trials but the objective response rates have been very limited [43]. In a phase I study with the combination of cixutumumab and mTOR inhibitor temsirolimus, only 42% of patients showed disease stability

for more than six months [44]. On the other hand, another trial reported partial responses in only 5% of patients when treated with the combination of cixutumumab and mitotane in the first-line setting [45]. Notably, despite having good responses in low-grade tumors, dual IGF-1R/insulin receptor inhibitor, linsitinib, failed to meet its primary endpoint of OS in a phase III randomized, placebo-controlled trial [46]. Overall, these data indicates that effective therapeutic exploitation may need biomarker-driven patient selection, more advanced combinatorial strategies, or next-generation inhibitors which are capable of overcoming pathway compensation. Although mTOR inhibitors have shown poor performance in advanced ACC, preclinical data suggests that these compounds synergize well with IGF axis inhibition. In addition, their combination with immunotherapy (e.g., eganelisib + nivolumab) has potential for multi-pathway targeting approaches [47]. The complexity of such an IGF-mTOR signaling targeted approach however illustrates the need for better strategies to limit the pathway cross-talk, resistance mechanisms, and tumor heterogeneity.

CTNNB1 mutations are highly prevalent in ACCs along with functional loss of ZNRF3, hence providing another attractive therapeutic avenue for the treatment of ACCs. Preclinical studies with small-molecule inhibitors of TCF/β-catenin complex (e.g., PKF115-584) or β-catenin knockdown have achieved effective reduction in proliferation and induction of apoptosis in ACCs [17]. These findings confirm the oncogenic dependency of ACC on Wnt signaling and provide proof of principle for pathway-directed interventions. However, the clinical translation of Wnt-targeting agents remains limited. The difficulty of achieving selective inhibition without significant off-target effects, given the pathway's essential role in normal tissue homeostasis, has hindered the development of clinically viable inhibitors. Moreover, the extensive integration of Wnt signaling with adrenal development and zonation pathways creates challenges in balancing therapeutic efficacy with preservation of endocrine function [20]. Despite these barriers, the identification of Wnt-activated molecular clusters within ACC and the availability of next-generation inhibitors targeting upstream regulators (e.g., porcupine inhibitors) suggest that Wnt-directed therapy may eventually find a role in biomarker-defined patient subsets or in combination with other pathway inhibitors.

TKIs constitute one of the most extensively explored classes of targeted therapies in ACC, given the strong biological rationale for targeting angiogenesis, growth factor signaling, and metastatic pathways. However, clinical outcomes across most VEGFR-focused TKIs have been variable and generally modest. Early trials of sorafenib, sunitinib, and axitinib demonstrated minimal anti-tumor activity (**Table 1**). In prospective phase II studies, all three agents yielded low disease control rates and median PFS values under three months, with no durable objective responses [38, 41, 48]. The unique vascular biology of ACC is responsible for limited efficacy of these treatment, as marked by vasculogenic mimicry, high stromal resistance, and activation of multiple compensatory angiogenic pathways [39, 49]. On the other hand, promising anti-tumor activity has been reported for cabozantinib, a multi-kinase inhibitor targeting VEGFR, MET, AXL, and RET. Partial responses and prolonged disease control along with median PFS of 6-16 weeks in heavily pretreated patients have been observed for cabozantinib treatment in ACCs in retrospective and early-phase studies [50, 51]. Broader inhibition of metastatic and invasive signaling pathways like MET and AXL signaling, is the key therapeutic advantage of cabozantinib treatment in ACCs, leading to active suppression of aggressive tumor behavior. Synergistic targeting of EGFR and IGF1R has also been fruitful in ACCs as shown by preclinical studies where combination blockade significantly reduced tumor growth relative to monotherapy [52]. Although these findings highlight dual-pathway blockade as a key advancement in overcoming resistance to single-agent TKIs, clinical evidence is still lacking. Taken together, while VEGFR TKIs show limited clinical benefit, cabozantinib treatment and the rational of combining multiple TKIs represent meaningful advances in the precision-therapy against ACCs.

Pioglitazone and rosiglitazone are well-established peroxisome proliferator-activated receptor gamma (PPARγ) agonists, which have shown considerable anti-tumor activity in ACC models. These agents not only promote apoptosis induction, reduce angiogenesis, and inhibit proliferative pathways, such as PI3K/AKT and ERK1/2, but also limit pro-survival signals including VEGF and Bcl-2 [53, 54]. Reductions in tumor volume and microvessel density along with an increase in CXCL12 expression, a chemokine associated with improved prognosis, have been observed with rosiglitazone treatment in animal models [55]. However, clinical benefit of these therapies in ACCs is still limited as the therapeutic potential of PPARγ modulation remains largely unexplored. Therefore, PPARγ agonists are attractive candidates to be tried as a treatment for ACCs in future combination regimens.

As cell-cycle deregulation and disruption of DNA damage response pathways are key pathogenesis mechanisms in ACC, targeting these pathways are of key importance. In CTNNB1-mutant cell lines, nutlin-3a, an MDM2 inhibitor, has shown great preclinical activity by inducing apoptosis and reducing hormone production [56]. On the other hand, BI-2536, a PLK1 inhibitor, has shown the ability to effectively restore p53 signaling, disrupt centrosome homeostasis, and induce apoptosis in ACC cells in vitro [57, 58]. CDK4/6 inhibitors (e.g., palbociclib, ribociclib), known for cell-cycle blockade, have also shown promising preclinical results by reducing cell viability and promoting senescence or apoptosis in ACC cells in vitro [59]. Treatment with PARP inhibitors, such as olaparib, rucaparib, and talazoparib is primarily supported by alterations in homologous recombination repair, though their efficacy in ACC remains to be fully validated.

Immunotherapy and immune modulators

Therapeutic landscape for various solid malignancies including ACC has been reshaped with the advent of immunotherapies and immune modulators (**Table 1**). Variable outcomes in ACC have been observed with monotherapy of ICIs targeting PD-1 or PD-L1, resulting in modest overall response rates relative to other solid tumors. In a multi-cohort phase Ib study, partial responses in 6% of patients and disease stabilization in 42% were observed with avelumab in ACC patients, which led to a median PFS of 2.6 months [60]. On the other hand, in a phase II trial with previously treated patients, nivolumab treatment stabilized the disease in only 20% of individuals but objective responses were not achieved, and rapid disease progression was observed after only a median of two doses [35]. Pembrolizumab treatment in ACCs has however shown more favorable activity in ACCs. It achieved partial responses in 14-23% of patients and disease control rates ranging from 41% to 64% in two independent prospective trials [36, 61]. These outcomes highlight that the overall responsiveness of ACC to checkpoint inhibition monotherapy is primarily modest. The reason behind this includes tumor heterogeneity to microsatellite instability, immune cell infiltration, and systemic cortisol levels. As discussed previously, ACC tumors have low tumor mutational burden, but a small subset of tumors display mismatch repair deficiency and MSI-H, often in the context of Lynch syndrome. These tumors are highly susceptible to ICI therapy [31]. In line with this, 33% of MSI-H patients achieved partial response and an additional 33% achieved durable stable disease for more than 24 months with pembrolizumab treatment [61]. Similarly, durable responses towards combination immunotherapies have also largely

been confined to patients with MSI-H tumors [37]. On the other hand, as the vast majority of ACC cases represent microsatellite-stability, monotherapy with ICIs is often associated with limited responsiveness in these patients. Overall, these findings highlight the need for molecular stratification, and MSI-H status can serve as biomarkers of immunotherapy efficacy in ACCs.

Combination therapies targeting CTLA-4 and PD-1 have shown promising immunologic activation in different cancer types including ACC. In this line, dual therapy with ipilimumab and nivolumab has shown partial responses in 19% and stable disease in 33%, with overall clinical benefit in 52% of patients in a rare tumor cohort of the CA209-538 study [37]. Despite this, the toxicities associated with CTLA-4 inhibition warrant careful patient selection, especially in cases where cortisol-secreting disease can lead to immunotherapy-related adrenal crises. Profound immunosuppression and aberrant angiogenesis characteristic of ACC also support the combination strategies integrating VEGFR-targeted agents and ICIs. In this line, a multi-cohort phase II study has evaluated the combination of cabozantinib with atezolizumab, and reported partial responses in 8.3% and durable clinical benefit in select ACC patients [62]. However, limited (2.9 months) median PFS was achieved in this study, mainly attributed to the inclusion of heavily pretreated patients. A phase II trial of camrelizumab plus apatinib combination achieved a 50% objective response rate and 95% disease control rate, with a median PFS of 12.6 months and median OS of 20.9 months. These compelling results substantially exceed the outcomes observed with monotherapy ICIs [63]. Mechanistically, increased tumor-infiltration of $CD8^+$ T cells, enhanced clonal overlap between circulating and intratumoral lymphocytes, and reductions in immunosuppressive $CD4^+$ cells, were the key behind synergistic effects observed with the combination of angiogenesis inhibition and PD-1 blockade [63].

ACCs exhibit high expression of IL-13Rα2 receptor, making it a promising target. Treatment with recombinant fusion toxin IL-13-Pseudomonas exotoxin (IL-13-PE) in a phase I study has shown disease stabilization for 2 to 5.5 months in IL-13Rα2-positive ACC patients [64]. On the other hand, CAR-T cell therapies against IL-13Rα2 have also shown considerable antitumor activity in preclinical studies with ACC cell lines [65]. Therefore, solid-tumor CAR-T engineering and receptor-directed cellular immunotherapy, particularly in combination with tumor microenvironment modulators, has become a key therapeutic frontier in ACC treatment. Immunosuppressive effects of endogenous cortisol have led to the therapeutic strategies entailing modulation of the glucocorticoid signaling axis in augmenting immunotherapy efficacy. In this context, relacorilant is a selective glucocorticoid receptor modulator. It has been shown to reverse cortisol-mediated immune dysfunction [66-68]. Currently, a phase Ib trial is evaluating the combination of relacorilant with pembrolizumab in cortisol-producing ACC. The aim of the study is to test whether this combination can restore T-cell function while simultaneously enabling effective checkpoint blockade. Promising results from the trials will serve as a base for the establishment of integrated immunotherapeutic strategy moving forward.

Next-generation precision modalities

Radiopharmaceutical approaches in ACC capitalize on the unique steroidogenic biology of adrenal cortical cells. ^{123}I-IMTO and its therapeutic analogue ^{131}I-IMTO exploit adrenal-specific binding to 11β-hydroxylase, enabling both diagnostic imaging and targeted radionuclide therapy. In a cohort of 49 patients, 27% demonstrated high ^{123}I-IMTO uptake, and among those treated with ^{131}I-IMTO, partial response or sustained disease stabilization was observed in 60% of evaluable individuals, with a median PFS of 14 months [69]. Broader target binding across metastatic lesions was observed with a subsequent generation agent, ^{131}I-IMAZA. Although only 19% of patients receiving this therapy showed strong uptake, 42% achieved considerable disease stabilization with a median PFS of 14.3 months [70]. Targeted therapy with ^{90}Y/^{177}Lu-DOTATOC has shown modest activity in patients with sufficient somatostatin receptor expression, though the expression of the receptor is not uniformly high in ACC. Two out of 19 patients have shown robust uptake and received radionuclide treatment in a prospective study. As a result, one of them developed a partial response lasting 12 months [71]. Such treatment approaches highlight the potential for highly selective molecular imaging to guide individualized therapy, though the treatment eligible population is small.

Antibody-drug conjugates (ADCs) offer another treatment frontier for targeted drug delivery by combining antigen specificity with cytotoxic payloads [72]. ABBV-176, which targets the prolactin receptor (PRLR), was evaluated in a phase I trial that included two ACC patients. Unfortunately, no substantial clinical responses were observed along with hematologic and hepatic toxicities, leading to early trial termination [73]. The Notch ligand DLK1 is overexpressed in ACC, leading to tumor stemness. ADCT-701, a pyrrolobenzodiazepine dimer-conjugated ADC, has been developed to target DLK1. Preclinical studies have shown potent antitumor activity in ACC xenografts [74]. On the other hand, ADCT-211, a next-generation PBD-based ADC targeting IL-13Rα2 receptor, has shown compelling preclinical efficacy along with complete tumor regression in ACCs [75]. Although hurdles like antigen heterogeneity, payload toxicity, and delivery optimization exist, ADCs are a promising class of precision therapies to limit ACC tumor burden with high specificity.

Amplifying T-cell responses against tumor-associated antigens by the use of therapeutic vaccines in ACCs is a key avenue to overcome the inherent lack of tumor immunogenicity in these tumors. In this line, EO2401 incorporates peptides that mimic ACC-associated antigens, such as IL13RA2, BIRC5, and FOXM1. Its combination with nivolumab in a phase I/II study has shown partial responses in 12% and disease stabilization in 24% of patients, though median PFS was reported to be just 1.9 months [76]. On the other hand, mRNA-0523-L001, an individualized neoantigen vaccine designed for endocrine malignancies including ACC, is also being tested in a phase I study. mRNA vaccines have the potential to become a highly personalized strategy with durable and potent immune responses by leveraging next-generation sequencing and patient-specific neoepitopes. Another rapidly expanding frontier in ACC treatment is cellular immunotherapies, primarily driven by lineage-restricted surface antigens and CAR engineering. ACC, along with multiple pediatric and adult solid tumors, express B7-H3. B7-H3-CAR-T cells have shown great antitumor activity in preclinical ACC models [77]. B7-H3 CAR-T therapy is being tested in pediatric solid tumors, including ACC, in a phase I trial. ROR1 is another tumor-associated antigen that is being explored in ACC. CRISPR-mediated glucocorticoid receptor knockout has been shown to enhance the antitumor activity of ROR1-CAR-T cells in preclinical ACC models. In line with this, IL-13Rα2-CAR-T cells have also shown tumor inhibition capacity in ACC preclinical studies [65]. Although clinical translation is still in early stages, CAR-T and cellular therapies, particularly in combination with microenvironmental modulation, represent a promising future for different subsets of ACC patients.

Advances in nanotechnology, bioengineering, and artificial intelligence (AI) have been instrumental to improve drug delivery, immune activation, and precision therapy in ACC. Delivery vehicles with copper-based nanomaterials and other engineered nanoparticles have shown promising results in enhancing intratumoral drug penetration and generating imaging contrast for ACC lesions. Tumor microenvironment modulating nanoparticles

have been shown to modulate stromal architecture and facilitate immunogenic cell death [78, 79]. Emerging bioengineering strategies have also shown systemic immunomodulatory effects in early studies, suggesting their role in altering stromal and immune cell activation patterns, and their synergy with immunotherapy [80]. AI has been applied to diverse cancer contexts [81], and holds enormous potential for ACC. Based on their ability to integrate multi-omics data, imaging biomarkers, and clinical variables, AI systems have shown potential to facilitate early diagnosis, patient stratification, and therapy selection, thereby playing an active role in the development of precision therapy.

Conclusion and future perspective

ACC represents a complex tumor subtype within endocrine oncology, mainly attributed to its biological diversity, therapy resistance, and poor clinical outcomes in nearly all stages of the disease. Although the field has moved steadily toward more biologically informed approaches, it is quite clear that many long-standing challenges still limit the translation of scientific progress into consistent clinical benefit. One major difficulty is that ACC is an exceptionally rare cancer, making it very hard to conduct sufficiently powered clinical trials, as most prospective studies include only a small number of highly heterogeneous patients [35, 37, 63]. Furthermore, ACC is not a single uniform entity but consists of several molecularly distinct subgroups, such as the COC1-COC3 clusters, that vary widely in their levels of proliferation, methylation patterns, immune infiltration, and steroidogenic activity [12]. Because of this complexity, responses to targeted therapies like IGF1R inhibitors, mTOR inhibitors, and various TKIs are often inconsistent. In addition, the tumor microenvironment is generally immunosuppressive due to low tumor mutational burden, minimal T-cell infiltration, and cortisol excess, which makes immune checkpoint blockade less effective except in the relatively rare MSI-H population. Conventional trial endpoints like ORR, PFS, and OS also fail to capture clinically meaningful disease stabilization sometimes. The lack of reliable predictive biomarkers for different treatments still limits our ability to choose the right therapy for the selected group of patients.

Notable progress has been made toward a more integrated, multi-dimensional treatment paradigm for ACC despite the above discussed limitations. Combination therapies are the key advancements that allow targeting of different biological vulnerabilities. VEGFR TKIs combined with PD-1 inhibitors, IGF1R with mTOR inhibition, epigenetic modulators with immunotherapy, or glucocorticoid receptor modulation with ICIs are all aiding in counteract multiple resistance pathways. Combining genomics, transcriptomics, proteomics, and endocrine profiling into a clinically meaningful framework represents the future of therapeutic treatment of cancer, in general, and ACC, in particular. This may involve expanding molecular classifiers similar to COC1-COC3 with additional immune and metabolic information. On the other hand, innovative trial designs, including adaptive platform trials, Bayesian models, and multinational collaborations, will be essential to evaluate emerging therapies more efficiently, as ACC represents a rare cancer type. Alongside this, AI has significant potential to contribute to predictive modeling, early relapse detection, and multi-omics integration [82, 83]. Therapeutic success can also be enhanced by targeting stromal and metabolic factors, such as SOAT1 [84], cholesterol trafficking pathways, or vasculogenic mimicry. Overall, integrating multi-omics insights with next-generation therapeutic technologies promises the development of individualized management strategies to tackle ACC in the future.

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Ethical policy

Non applicable.

Availability of data and materials

All data generated or analysed during this study are included in this publication.

Author contributions

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Competing interests

The author declares no competing interests.

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