# Clinical Development in Challenging Cancers: Adrenocortical Carcinoma

PEER REVIEWED

## Overview of disease

Adrenocortical carcinoma (ACC) is a rare cancer with an estimated incidence of 1 to 2 patients per million people annually,[1-3] and one in which most patients, at diagnosis, already present with a locally advanced or metastatic disease not suitable for surgery.[4] Age distribution for this disease follows a bimodal pattern, with an initial peak in childhood, and a subsequent peak in adults between the fourth and fifth decades[5] (Fig. 1). Higher incidence rates (3–4 cases per million annually) have been described in Southern Brazil, particularly in children below the age of 15 years.[6] While genetic aberrations may predispose to adrenal cortical tumour formation, it has been suggested that environmental factors, such as pesticides used in agricultural activities, also play a pivotal role in tumorigenesis in Southern Brazil,[6] given that the distribution of the disease follows a regional rather than familial pattern.[7]

About 50%–70% of adrenal cancers are functional, i.e. hormone-secreting, and are mostly discovered as a result of clinical manifestations of hormonal syndromes (feminisation in men, virilisation in women) and metabolic syndromes (hypercortisolism). Others, instead, have a more silent clinical presentation and are detected only when they grow to dimensions large enough to produce localised abdominal symptoms.

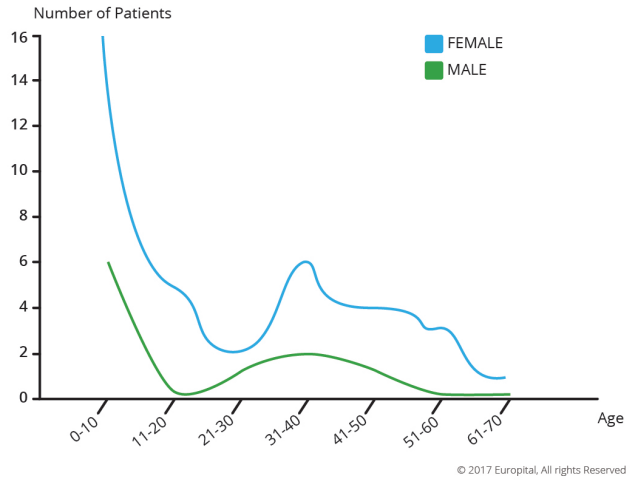




*Fig. 1; Bimodal distribution of adrenocortical cancer by age group**
**Data for this figure was culled from Wajchenberg et al.[46]*

## Treatment of ACC

### Current Therapies – Mitotane

Advances in the medical treatment of patients with ACC have been unpromising, owing mainly to difficulty in diagnosis and to minimal response of ACC to antineoplastic agents, not unlike other endocrine tumours. For years, medical treatment for adrenal cancer has been dependent on standard chemotherapy with mitotane, an isomer of the insecticide Dichlorodiphenyltrichloroethane (DDT), which possesses adrenolytic and anti-steroidogenic action.[8-9] In addition to its adrenolytic effects, mitotane inhibits MDR-1/P-glycoprotein, a multidrug resistance protein largely expressed in ACC, thus enhancing the effect of different chemotherapy drugs.[10] Mitotane alone or in combination with other cytotoxic drugs including cisplatin, streptozotocin, etoposide and doxorubicin, among others, has been adopted as a mainstay in the medical treatment of ACC, particularly in patients with advanced cancer.[11-12] Treatment regimens with mitotane, however, typically combine hydrocortisone and fludrocortisone replacement therapy where patients present adrenal deficiency.[13]

In a bid to validate the gold standard for treatment of advanced ACC, the First International Randomized Trial in locally Advanced and Metastatic Adrenocortical Carcinoma Treatment (FIRM-ACT Study) was initiated in 2004. This multinational study, a first of its kind, sought to compare a combination of etoposide, doxorubicin, cisplatin and mitotane (EDP-M arm) or streptozotocin and mitotane (Sz-M arm) as a first-line treatment for patients presenting with stage III or IV ACC.[14]

Results from this study showed that patients receiving the EDP-M regimen demonstrated a significantly higher response rate than those treated with the Sz-M regimen (23.2% vs 9.2%),[14] with longer median progression-free survival (PFS) (5.0 months vs 2.1 months), thus establishing EDP-M as standard initial therapy for patients with advanced ACC. No significant difference, however, was noted in median duration of overall survival (OS) (14.8 months vs 12 months).[14] To date, there is no approved second-line treatment for patients who experience a disease progression on these agents, although a combination of gemcitabine and capecitabine has proven to be beneficial in these patients, and has been proposed as second-line treatment in heavily pretreated ACC patients.[15]

The results from the FIRM-ACT study underlined the imperative need to discover other molecular pathways in disease pathogenesis and potential targets, and to seek more effective treatments in the clinical management of ACC.

## Targeted Therapies

Similarly to most rare diseases, the genetic component in adrenocortical cancers is very pronounced and potential treatment regimens are constantly being explored based on the analysis of genomic mutations identified in tumour samples from patients.

Over the past few years, advances in the understanding of these mutations have led to the identification of several potential molecular targets for selective therapy of ACC.[16] Approximately fifty different driver genes have been implicated in the development of ACC, including, among others CTNNB1, TP53, RB1, CDKN2A and MEN1.[16] Other genes less commonly linked to ACC include ZNFR3, DAXX, TERT and MED12.[17] Many of these have been employed and are still being developed as target therapies but very few have actually delivered any significant results. Table 1 lists ongoing clinical trials recruiting patients with ACC, per ClinicalTrials.gov, February 7, 2017.

| Study Number | Design | Compound | Mechanism of Action |
|---|---|---|---|
| NCT02720484 | Phase II, open label | Nivolumab | anti-PD-1 monoclonal antibody |
| NCT02673333 | Phase II, open label | Pembrolizumab | anti-PD-1 monoclonal antibody |
| NCT01898715 | Phase I, open label | ATR-101 | Inhibitor of sterol O-acyltransferase 1 |



*Table 1: Ongoing Studies Currently Recruiting Patients Exclusively with ACC*

**Receptor Tyrosine Kinases (rtk)**

**IGF-1R**

Overexpression of insulin-like growth factor 2 (IGF2) has been identified as an important molecular marker of adrenocortical cancer, occurring in over 90% of ACC tumours.[18] This excessive secretion of IGF-2 results in unchecked proliferation, migration and metastasis of ACC cells (as well as other cancers) through the IGF-1 receptor.[17-18]

Small-molecule tyrosine kinase inhibitors of this receptor have been developed; lensitinib (OSI-906) was studied in an open-label, Phase I study,[19] and in a double-blind placebo-controlled Phase III trial of 139 patients with locally advanced or metastatic ACC to evaluate the feasibility and efficacy of OSI-906 (GALACCTIC Study).[20] This latter study, however, failed to demonstrate a significant difference in median overall survival (OS) or progression-free survival (PFS), when compared with placebo.

**EGFR**

Similarly, epidermal growth factor receptors (EGFRs) have been found to be expressed in about 80% of cases.[21] The role of two tyrosine kinase inhibitors has been evaluated; erlotinib was studied in combination with gemcitabine in 10 patients with advanced ACC. Results from this study were disappointing, with nine patients out of 10 presenting a median survival of 5.5 months after commencing treatment.[22] Gefitinib, another EGFR TKI, was studied in a Phase II trial of patients with unresectable ACC. Of the 19 evaluable patients, none presented an objective response or stable disease.[23]

**VEGFR**

Even less encouraging results were obtained in clinical studies employing other small-molecule tyrosine kinase inhibitors targeting VEGFR, such as sorafenib and sunitinib.[16] Sorafenib, in combination with metronomic administration of paclitaxel was studied in a multi-centre Phase II study of 25 patients with metastatic ACC who had progressed on mitotane and at least one prior cisplatin-based chemotherapy regimen.[24] The trial was prematurely interrupted after all evaluable patients (9/9) had disease progression on their first eight-week evaluation. In a Phase II, single-arm, open-label trial of sunitinib in 35 patients with advanced ACC, 24 of these patients had progressive disease and six of them died ahead of the first assessment at 12 weeks, while only five had stable disease.[25]

**mTOR**

The mechanistic target of rapamycin (mTOR) is a member of the PI 3-kinase family of protein kinases involved in cell growth and proliferation and several studies indicate its importance as a potential therapeutic target for ACC.[26-28] Temsirolimus, an mTOR inhibitor, was studied in combination with cixutumumab, an anti-IGF-1R recombinant monoclonal antibody, in 26 patients with metastatic ACC. Reportedly, 11 of the 26 patients (42%) achieved stable disease (SD) > 6 months (duration range => 6–21 months).[29] Based on these results, larger studies in this population of patients and with this drug combination should be advanced.

**Future Prospects**

The role of immunotherapy for medical management of ACC is currently under study. Attempts to elicit T-cell response to tumour cells through blockage of the programmed cell death (PD) pathway have proved to be quite successful in several solid tumours.[30-31] Presently, a Phase I, open-label study of avelumab, an anti PD-ligand 1 is currently recruiting participants and is open to patients diagnosed with adrenocortical cancer (NCT01772004).

High expression of survivin, the smallest member of the inhibitor of apoptosis (IAP) family of proteins, has been associated with poorer prognosis in a cohort of 29 ACC patients.[32] Some authors have suggested that development of treatment regimens using survivin as immune checkpoint blockade (PD-1) should be considered for an efficient anti-tumour immune response and implemented in clinical trials.[33]

A recently concluded study examined genomic profiling of ACC tissue from 91 patients derived from four continents, representing a near-global sampling of the disease.[34] According to the authors, the cohort studied is the largest to be sequenced to date, though a much larger number of samples will be required to identify all candidate genes. In this study, alterations of many of the already known driver genes, such as overexpression of IGF-2, and mutations of TP53, ZNFR3, CTNNB1 were confirmed as essential for ACC development and progression. The study also identified several novel molecular pathways associated with deregulated genes. Inactivating mutations of the protein kinase cAMP-dependent regulatory type I alpha gene (PRKAR1A) were observed in about 8% of the cases in this cohort. Two frameshift mutations and a third in-frame deletion mutation in ribosomal protein L22 (RPL22) were detected, suggesting a role for somatic alteration of RPL22 in 7% of patients with ACC.[34]

Findings from this study have reportedly expanded the somatic genetic landscape of ACC to nearly double the already known driver genes. Also, based on a review of clinical trials and FDA-approved cancer drugs, the authors identified 51 genetic alterations that represent potential targets for new therapeutics.[34] Moreover, analyses revealed whole-genome doubling (WGD) as a common characteristic of ACC, reflecting the instability of the cancer genome and confirming this phenomenon as a key milestone in ACC disease progression. Furthermore, the authors extended the molecular classification of ACC from two to three classes that have markedly distinct biological properties and significantly different patient outcomes.[34] The authors conclude that this diversity of genomic alterations suggest that combined inhibition of disease pathways holds the key to successful targeted therapy for ACC.

Molecular profiling (MP) of tumours to identify markers that most accurately predict outcomes is an emerging approach in guiding treatment decisions. In a recent study on the use of this strategy to guide therapy, it was observed that 34 out of 54 patients (95% confidence interval 44–76%, $p < 0.0001$) obtained clinical benefit (based on investigator-assessed response or PFS ratio) from MP-guided therapy.[35] The authors also note that MP offers an opportunity to use conventional chemotherapy in a targeted manner. Table 2 shows a list of potential targets that, according to published data, have shown promising results.

| Compound | Mechanism of action | Results from pre-clinical studies (in vitro) | Comments |
|---|---|---|---|
| Interferon-beta [37] | Blockage of the S-phase of the cell cycle | Inhibition of cell growth and cortisol production | Alone or in combination with mitotane |
| Temozolomide [38] | DNA-alkylating agent | Induction of cell cycle arrests in ACC cell lines. | |
| HSP90 inhibitor AUY922 [39] | Heat Shock Protein | Inhibition of cell proliferation and induction of apoptosis in ACC cells linesin a time- and dose-dependent manner | "specific cell lines" |
| Decitabine [40] | Nucleic Acid Synthesis Inhibitor (DNA methyltransferase inhibitor) | Significant time-dependent cytostatic attenuation of ACC cell proliferation | "specific cell lines" |
| Aclarubicin TOP 2A inhibitor [41] | Anthracycline drug Induction of histone eviction from chromatin | Significantly decreased proliferation and tumor spheroid size in ACC cell lines | Already approved as a second-line therapy for acute myelocytic leukemia |
| Interleukin-13 receptor alpha2 (IL13Rα2) [42] | | Significant reduction in tumor size and tumor necrosis compared to control groups | Phase I trial done already [43] |
| Wnt/B-catenin inhibitors (PKF115–584) [44] | | Apoptosis in ACC cell lines with B-catenin mutations | |
| Co-inhibition of EGFR and IGF 1 receptor [45] | | This combination regime enhances anti-tumor efficacy compared to treatment with either agent alone or to untreated control in vitro and vivo | |



*Table 2: Potential Targets Presently Being Considered*

**Closing Remarks**

As discussed above, several targeted therapies have been investigated within the context of small-scale trials but have all failed to demonstrate clear clinical advantage or significant improvement in overall survival. In their recently published review, Kerkhofs and colleagues observed that the interpretation of results from these trials is rather difficult owing to several reasons.[36] Patients enrolled into these clinical trials have been likely pretreated with mitotane and the tumours may present some form of resistance to the compound being studied. Pre-treatment with mitotane and the consequent CYP3A4 induction might also impair the effectiveness of the therapies studied.[36]

An important question therefore arises as to whether overall effect on survival in clinical studies might be valid within specific subgroups of patients.

In their study, Zheng *et al.* observed that the three subtypes of ACC hold significantly different outcomes for patients, proposing a strategy for clinical stratification of patients based on molecular markers.[34]

Kerkhofs *et al.* argue that future trials should consider stratification of patients, not only based on tumour characteristics, but also based on disease progression and that patients with advanced ACC and naïve to systemic therapy could be considered a suitable subgroup.[36]

In all, these findings advocate for a greater focus on patients' subgroups, with planned stratification of study subjects enrolled into future clinical trials of ACC, as this might help determine the best course of treatment for each patient.

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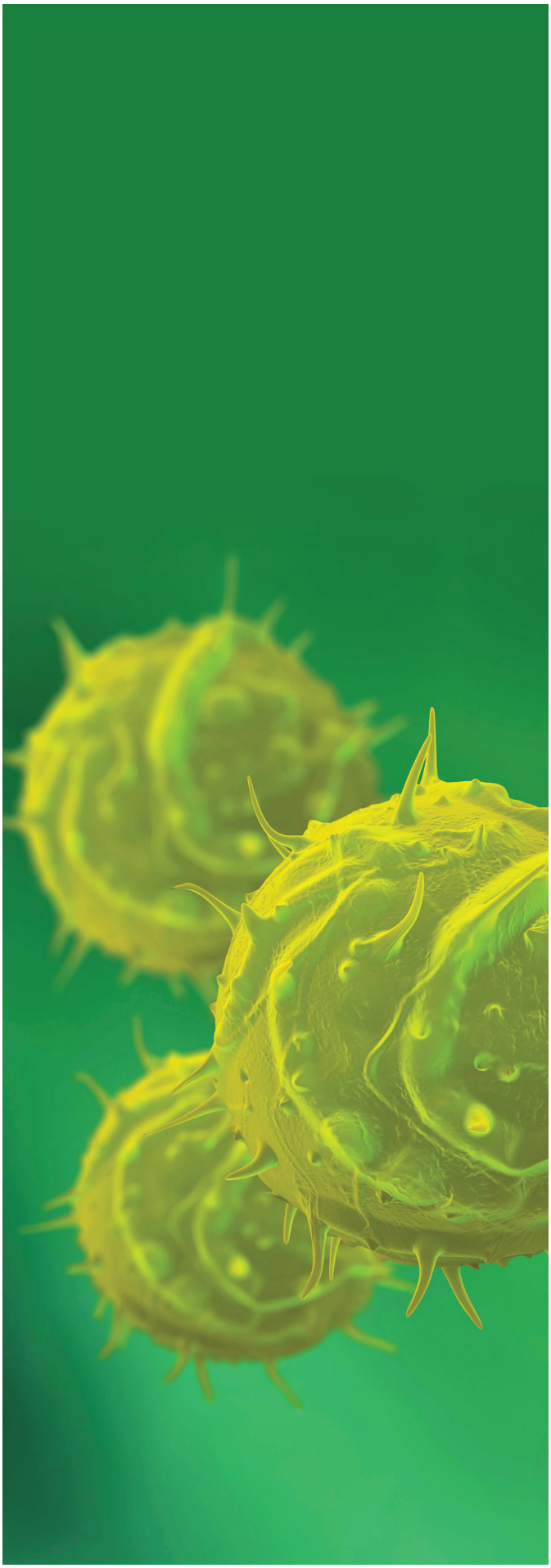

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## Kelechi K. Olu MD, MSc

Physician with strong research interests, Dr. Olu has garnered considerable experience in various aspects of clinical drug development and post-marketing surveillance, and in clinical research at large. As a clinical epidemiologist, Dr. Olu has also worked extensively on several research projects investigating underlying factors that lead to premature discontinuation of approved clinical trials.

**Email: info@europital.com**

## Vijayanand Rajendran, MD

Senior Clinical Research Physician, Europital. Qualified physician with over nine years of clinical and research experience. Hands on experience in safety monitoring of Phase I–IV trials in a variety of therapeutic areas including oncology, haematology, gastroenterology and the musculo-skeletal system.

**Email: info@europital.com**

## Mohamed El Malt, MD, PhD

Chief Medical Consultant, Europital. Oncology surgeon and expert scientific researcher with more than 32 years of experience as a medical doctor, including 18 years of clinical research and drug development experience in academic medical centres, pharma and CRO as investigator, project leader and medical director, in addition to 15 years of experience as general and oncology surgeon.

**Email: info@europital.com**