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Emerging therapy for adrenocortical carcinoma

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Abstract

Adrenocortical carcinoma (ACC) is a very rare and aggressive tumor with dismal outcomes. Best current treatments include complete surgical resection for localized resectable disease and systemic therapy with mitotane alone or in combination for advanced ACC. Advances in molecular genetic profiling of ACC have created multiple new targets for potential treatment options in ACC. This article reviews the current treatment options available for ACC and discusses the potential new targets identified through molecular profiling.

Keywords

adrenocortical carcinoma; genomics; molecular profiling; systemic treatment

Adrenocortical carcinoma (ACC) is a very rare tumor with an annual incidence of 1–2 cases per million. The long-term outcomes for ACC are poor with a 5-year survival rate of 35% in most series [1-4]. While stages III and IV have a dismal prognosis, localized disease has potential for cure with complete surgical resection [5]. Yet, even with an R0 resection, 50–80% of patients develop recurrent or metastatic disease [6,7]. Although complete surgical resection with negative margins remains the treatment of choice in localized ACC, the role of surgery in patients with recurrent and metastatic disease remains controversial. Most of the data regarding surgery in patients with recurrent or metastatic ACC are derived from retrospective reviews of single institutions. A recent study by Erdogan and colleagues compared clinical outcomes in ACC recurrent patients who underwent surgery with recurrent patients who did not have surgery [8]. They concluded that progression-free survival (PFS) was improved if the time to first recurrence was greater than 12 months and if patients were able to undergo an R0 resection for their recurrence [8]. Although a debulking surgery (R2 resection) did not significantly improve PFS, R2 resection did provide a modest benefit in overall survival compared with patients who did not undergo surgery (22 month vs 11 month) [8]. Other studies have also shown a survival benefit to surgical resection if the disease-free interval was greater than 1 year [9]. Metastasectomy in advanced ACC has provided some benefit for patients. Datrice *et al.* reported a 41% 5-year

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survival among 57 patients with metastatic ACC who underwent metastasectomy. The median survival for the cohort was 2.5 years months–12 years) [9]. Gaujoux and colleagues found similar results. In their cohort of 28 patients with metastatic ACC to the liver who underwent resection, they observed a median overall survival of 31.5 months and a 39% 5-year survival rate [10]. Several retrospective studies also identified a similar survival benefit with pulmonary resection for metastatic ACC [11,12]. An aggressive surgical approach for advanced ACC has been advocated in selected patients with more indolent disease since systemic treatment options are very limited. However, the interpretation of these retrospective studies is often difficult owing to a lack of comparable control group and patient selection. The majority of patients in these cohorts who underwent surgery often had less aggressive tumor compared with those in the 'control group' with unresectable tumor. This emphasizes that patient selection for surgery should be based on tumor biology. Mitotane has been the backbone of systemic treatment for advanced ACC until recently when a combination therapy of mitotane with etoposide, doxorubicin and cisplatin showed an improved response rate [13]. The objective of this review is to highlight the current systemic treatment for ACC and discuss the advances in molecular profiling that have led to new trials focusing on targeted therapies and the discoveries of potential new therapeutic targets for ACC.

Systemic chemotherapy

Chemotherapy options for ACC are limited. Mitotane, the only US FDA-approved agent for ACC, is an adrenolytic agent derived from the insecticide dichlorodiphenyltrichloroethane. Mitotane alone or in combination has been the standard treatment offered to patients with advanced stage ACC for decades. However, the response rates are dismal at only 30% and the toxic side effects make it difficult for patients to tolerate [14-16]. Discontinuation of mitotane-based therapy because of the toxicities is common. Haak *et al.* showed an objective tumor response in 15 of 27 patients treated with mitotane who maintained serum levels above 14 mg l^{-1}. They found no tumor response in patients with serum levels of mitotane less than 14 mg l^{-1} [14]. The ability to reach serum levels of 14 mg l^{-1} is difficult, especially in the setting of combination therapy. Some advocate for a high-dose approach to mitotane monotherapy and a low-dose approach when mitotane is combined with other cytotoxic drugs [17]. The use of mitotane in combination with standard cytotoxic agents has been investigated with the most common regimens being mitotane + streptozocin (M-Sz) or mitotane + etoposide/doxorubicin/cisplatin (M-EDP). A Phase II trial by Khan *et al.* exhibited a 36% response rate in patients with advanced ACC receiving M-Sz [18]. Berruti and colleagues reported a 53% response rate in patients receiving M-EDP [13]. Recently the FIRM-ACT trial comparing M-Sz and M-EDP was released. This was a landmark randomized controlled trial in 304 patients with advanced ACC [19]. The trial stated that M-EDP was superior to M-Sz with respect to objective tumor response, PFS and proportion of patients without progression at 1 year. In total, 23.2% of patients with M-EDP had tumor response compared with 9.2% of patients with M-Sz. The PFS was 5.0 months for M-EDP and 2.1 months for M-Sz. There was no significant difference in overall survival between the two groups at the study's conclusion [19]. Despite an improvement in response rates

with M-EDP, it was a toxic regime with 58.1% of patients experiencing serious adverse events [19].

Systemic therapy has a clear role in advanced or metastatic ACC. However, the role of mitotane as adjuvant therapy is less clear and has led to several studies investigating the use of mitotane as postoperative adjuvant therapy in ACC. Terzolo *et al.* reported a significantly prolonged recurrence-free survival in patients receiving mitotane compared with the two control groups without treatment (42 months vs 10 months and 25 months, respectively) [20]. A retrospective review from MD Anderson Cancer Center (TX, USA) reported that a "lack of adjuvant mitotane" treatment was a predictor of increased risk of recurrence on multivariate analysis [21]. Fassnacht and colleagues reported an improved 5-year survival among patients treated with adjuvant mitotane compared with patients not treated with mitotane (87% vs 53%, $p = 0.04$) [7]. The 5-year disease-specific survival was 64.1% and overall survival was 52% among patients receiving adjuvant mitotane after surgical resection [22]. Recently, Else and colleagues retrospectively analyzed a large cohort ($n = 391$) and found that patients who received adjuvant mitotane ($n = 105$) had a significantly improved recurrence-free survival with no impact on overall survival [23]. Bertherat *et al.* initially reported an improved survival in 202 patients receiving adjuvant mitotane within 3 months of surgical resection [24]. However, upon further analysis of the 166 patients in that cohort who underwent complete surgical resection, only 52% were treated with adjuvant mitotane. Univariate and multivariate analysis failed to indicate a benefit in disease-free survival among patients receiving adjuvant mitotane [25]. The difference in outcome among these studies is likely due to multiple factors, such as heterogeneous population and selection bias. The controversy over the true benefit of adjuvant mitotane in resected ACC will likely continue until the results of the ADIUVO trial are available. This study aims to assess the efficacy of postoperative adjuvant mitotane in reducing recurrence rates among low to intermediate risk patients with ACC [26].

Molecular oncogenesis of ACC & targeted therapy

Research into the oncogenesis of ACC has increased our understanding of the molecular mechanisms from genomic studies involved in ACC tumor initiation and progression. Potential biomarkers have been identified to aid early diagnosis, improve prognostication and may serve as targets for new drug development [27]. These advances indicate the importance of genetic dysregulation in ACC development [28,29] Pan-genomic analysis of genetic mutations, chromosomal aberrations, DNA methylation, gene expression or microRNA dysregulation can provide essential data that are key to improving the application of personalized treatment for patients with ACC and other cancers [27]. Work by De Martino *et al.* using hot spot gene sequencing and comparative genomic hybridization identified copy number alterations or genetic mutations in 47.5% of ACC patients [30]. In total, 40% of patients had abnormal regulatory mechanisms in the G1→S-phase of cell cycle progression suggesting that the cell cycle may be a possible therapeutic target to investigate [30]. Gene expression profiling of adrenocortical tumors has helped to differentiate between benign and malignant tumors. Velazquez-Fernandez *et al.* found clearly different molecular signatures between adrenocortical adenomas and carcinomas [31]. Over 500 genes were significantly differentially expressed between ACC and adrenocortical adenomas ($p < 0.01$)

[31]. Ubiquitin-related genes and several insulin-like growth factor-related genes were significantly upregulated in ACC. Several genes that regulate cell metabolism, (*RARRES2, ALDH1A1, CYBRD1*, and *GSTA4*), a cytokine (CXCL10) and cadherin 2 (CDH2) were all significantly downregulated in ACC [31]. Gene expression analysis has been used to identify molecular diagnostic and prognostic markers in ACC [1,32]. de Reynies *et al.* showed that benign adrenocortical tumors could be distinguished from malignant tumors using microarray technology [1]. In addition, they also showed that malignant tumors could be further divided into two different groups with different outcomes based on their molecular profile. Tumors with the combined expression of *DLG7* and *PINK1* had better disease-free survival and tumors with combined expression of *BUB1B* and *PINK1* had the best overall survival [1]. Giordano and colleagues displayed gene expression differences between early and late-stage ACC. On a multivariate Cox regression model gene expression remained a significant prognostic indicator of survival that was independent of tumor stage [32]. Recently, alterations in the retinoblastoma gene (*RB1*) have been described in ACC and may play a role in determining the aggressiveness of the tumor biology [33]. Immunohistochemistry displayed a loss of the retinoblastoma protein in seven of the 26 poor outcome ACCs and in none of the 20 ACCs with better outcomes [33]. Predicting outcomes and prognosis for patients with ACC is crucial for patient care and a current investigation into microRNAs in ACC has identified new potential biomarkers that are predictive of ACC prognosis. Chabre and colleagues reported significant overexpression of miR-483-5p and lower expression of miR-195 in ACC compared with adrenocortical adenoma, consistent with work published by Patterson *et al.* [34]. Patterson and colleagues used microarray profiling of benign and malignant adrenal tumors. They found that miR-483-5p was significantly upregulated in ACC compared with benign adrenal tumors and that the expression of miR-483-5p can accurately predict which adrenal tumors are malignant [35]. In addition, increased circulating levels of miR-483-5p and decreased circulating levels of miR-195 were associated with poor survival outcomes in patients with ACC [34,36]. The information obtained from gene expression profiling and analysis of micro-RNA has provided new markers of malignancy and increased our understanding of aberrant signaling pathways allowing for potentially new targeted therapies [1,27,31,35,37-40].

IGF-1R antagonists

Molecular profiling demonstrates that the *IGF-2* gene is significantly upregulated in approximately 90% of ACC compared with normal adrenals [1,29,31,37,41]. ACC tumors have also been shown to have high expression levels of the *IGF-1R* protein. [42] Upregulation of *IGF-2* and overexpression of *IGF-1R* suggest an important role in the activation of the IGF pathway and tumorgenesis of ACC. Barlaskar *et al.* identified a 60-fold increase in *IGF-2* expression of ACC compared with adenomas [43]. On tissue microarray analysis the group demonstrated a marked increase in signal intensity of phospho-IGF-1R and phospho-Akt in ACC compared with adenomas confirming overexpression of *IGF-2* and *IGF-1R* and activation of the downstream effector Akt [43].

Understanding the role of the IGF pathway in ACC pathogenesis has led to preclinical and clinical studies with IGF1R antagonists. *In vitro* and *in vivo* studies demonstrated decreased ACC cell proliferation and tumor growth inhibition when treated with IGF-1R antagonists

[43]. Haluska and colleagues performed a Phase I trial with the anti-IGF-1R monoclonal antibody figitumumab. In their study eight of 14 (57%) patients with advanced ACC treated with figitumumab had disease stability. Four patients had tumor shrinkage that did not meet clinical RECIST criteria for partial response [44]. The randomized double-blinded, placebo-controlled Phase III study of OSI-906 (a small molecule tyrosine kinase inhibitor directed against IGF-1R) in patients with locally advanced or metastatic ACC (GALACCTIC trial) has just been completed. Patients were randomized to placebo or treatment with OSI-906. The results of this trial are pending publication.

mTOR antagonists

The mammalian target of rapamycin (mTOR) is a protein kinase that is involved with cell growth and proliferation. It is activated in part by IGF-1R through the PI3K-Akt pathway and has been studied recently in cancer as a potential targeted therapy [45,46]. *In vitro* and *in vivo* mouse studies by Doghman *et al.* demonstrated that inhibition of mTOR signaling reduces adrenocortical tumor growth [47]. However, several studies have shown that mTOR inhibitors activate Akt through an IGF-1R-independent mechanism resulting in reduced antitumor effects of mTOR inhibitor and suggesting that IGF-1R inhibitors may reduce the Akt phosphorylation caused by mTOR inhibitors [48,49]. These findings support the rationale of combining mTOR inhibitor with an IGF-1R inhibitor to achieve additive antitumor effects in ACC [50]. A Phase I trial of cixutumumab (anti-IGF-1R antibody) in combination with temsirolimus (mTOR inhibitor) for patients with advanced cancer found tumor reduction in four of 10 patients with ACC [51]. Combination therapy of cixutumumab and temsirolimus resulted in a greater than 6 month stability of ACC in 42% of patients receiving treatment [52]. One-third of ACC patients treated with combination temsirolimus and lenalidomide (immunomodulatory drug with antiangiogenic properties) had disease stability greater than 6 months in a Phase I trial for patients with advanced cancer [53]. Further investigation into combination therapy of an mTOR inhibitor and an IGF-1R inhibitor is warranted based on early Phase I data.

Receptor tyrosine kinase inhibitors

Tyrosine kinase inhibitors have become important targeted therapies for cancer. The molecular profiling of ACC has revealed upregulation or overexpression of several receptor tyrosine kinases [54-59]. EGFR is expressed in more than 75% of ACC tumors [54,55,57]. Bernini *et al.* found a significantly higher expression of VEGF in ACC than in adrenal adenomas [59]. The overexpression of EGFR and VEGF has made receptor tyrosine kinase inhibition an attractive targeted strategy for the treatment of ACC. However, the results to date have been disappointing. In a Phase II trial, single agent Gefitinib, an EGFR antagonist, failed to demonstrate activity in 19 patients with advanced ACC [60]. Combination therapy of erlotinib and gemcitabine was also unsuccessful at preventing tumor progression in eight of 10 patients with advanced ACC [61]. Anti-VEGF antibody bevacizumab in combination with capecitabine provided no objective response or stability of disease in 10 patients with advanced ACC [62].

Multikinase inhibitors have also been evaluated as potential new therapies in ACC. A Phase I study reported disease stability in two patients with advanced ACC treated with sorafenib and tipifarnib (farnesyltransferase inhibitor) and a case report described a 28 month sustained response to sorafenib in a patient with metastatic ACC [63,64]. Despite encouraging early data, a recent Phase II study of sorafenib with paclitaxel was terminated early owing to disease progression in nine of 25 patients with advanced ACC at the first assessment after starting treatment [65]. Sunitinib also inhibits multiple receptor tyrosine kinases. A partial response was noted in a patient with metastatic ACC who was treated with sunitinib after failing cytotoxic chemotherapy. The response was achieved in 4 months, however after 7.5 months the patient experienced tumor progression [66]. A Phase II trial of sunitinib in refractory ACC demonstrated disease stability in five of 35 patients for a 15.4% response rate and median PFS of 2.8 months. In the patients who responded to sunitinib the median PFS was between 5.6 and 11.2 months with an overall survival between 14 and 35.5 months [67]. Even though preclinical data for tyrosine kinase inhibitors were promising, clinical studies have failed to demonstrate durable, long-term response in patients with advanced ACC. The lack of clinical response to tyrosine kinase inhibitors may be partially due to increased CYP3A4 activity from mitotane. Several studies have shown that mitotane induces the CYP3A4 system making it difficult to achieve appropriate serum drug levels. Tyrosine kinase inhibitors are also metabolized by the CYP3A4 system, suggesting that the serum concentrations of tyrosine kinase inhibitors may have been below adequate serum drug levels. The previous studies using tyrosine kinase inhibitors did not monitor drug concentration levels and future clinical trials that may incorporate or use tyrosine kinase inhibitors should consider serum drug concentration monitoring and dose modification as needed [68,69].

Future targets for novel therapy

Wnt/β-catenin pathway

Microarray analysis shows upregulation of the Wnt/β-catenin pathway [70,71]. The *CTNNB1* gene, which encodes β-catenin, is mutated in adrenal tumors [71,72]. The main event in pathogenesis of ACC may be related to activation of β-catenin and its nuclear localization. Moreover, the nuclear localization of β-catenin has been identified as a predictive factor associated with poor prognosis [73,74]. Preclinical studies using a transgenic mouse model have linked β-catenin activation to adrenal cortical dysplasia [75]. Furthermore, PKF115–584, a small molecule inhibitor of T-cell factor/β-catenin complex, has inhibited cell proliferation and induced apoptosis in NCI-H295R ACC cell lines [76]. Further studies of targeted therapies directed at this pathway are required.

Steroidogenic factor-1

Steroidogenic Factor-1 (SF-1) is a nuclear transcription factor involved with adrenocortical cell proliferation and steroidogenesis [77]. An increased overexpression of SF-1 in pediatric adrenal tumors has peaked interest in the role of SF-1 in tumor development [78]. Doghman and colleagues demonstrated that SF-1 regulates cellular proliferation, apoptosis, angiogenesis, adhesion to the extracellular matrix, cytoskeleton dynamics, transcriptional and post-transcriptional regulation of gene expression in adrenocortical cells [79]. Patients

with increased expression of SF-1 had a worse prognosis compared with patients with lower expression of SF-1, suggesting its prognostic implication [80]. Recently SF-1 inverse agonists have been shown to selectively inhibit proliferation in the H295R ACC cell line with increased expression of SF-1 [77]. Targeting SF-1 can reduce cortisol production and may provide symptom relief for patients with ACC-associated hypercortisolism, in addition to anti-tumor effect.

PPARγ antagonists

PPARγ is a nuclear transcription factor expressed in the adrenal cortex of normal tissue and in adrenal tumors [81,82]. Thiazolidinedione is a class of drugs that are ligands for PPARγ. Rosiglitazone is a thiazolidinedione that has been shown to have antiproliferative effects on several different cancers [83]. *In vitro* and *in vivo* data demonstrate that thiazolidinediones have an antiproliferative effect on ACC cells [81,82,84-86]. Luconi *et al.* showed that treatment with rosiglitazone resulted in a significant reduction in tumor growth in the treated mice compared with the control group. In contrast to aggressive and more invasive tumors with abundant vascular network and high mitotic figures found in the control group, the tumors of the rosiglitazone-treated mice displayed a noninfiltrating margin, smaller vessels and apoptotic cells [86]. Despite the promising results from preclinical work, the true mechanism responsible for decreased proliferation by rosiglitazone is not completely understood. Preclinical data suggest that rosiglitazone works through both PPARγ-dependent and PPARγ-independent pathways to cause growth arrest, cell death and decreased neovascularization [81,84,85]. Rosiglitazone inhibits ACC cell proliferation by interfering with Akt and ERK1/2 phosphorylation mediated by IGF-1 [84]. PPARγ antagonists may hold potential as a future treatment option for ACC.

Selective estrogen receptor modulators

Normal adrenal cortical tissue and adrenocortical tumors express aromatase, estrogen receptors alpha and beta (ERα, ERβ) and androgens [87]. Aromatase is essential for peripheral conversion of androgens to estrogens. Barzon *et al.* demonstrated overexpression of aromatase in adrenocortical tumors. They also showed, through immunohistochemistry, that ERβ has a twofold greater expression than ERα in normal adrenal tissue. However, in ACC tumors the ratio of ERα/ERβ was increased indicating an overexpression of ERα in adrenocortical carcinoma [87]. An *in vitro* study of NCI-H295R ACC cell line demonstrated that ACC cells are capable of converting androgens to estrogens via aromatase. The newly converted estrogens may regulate cell proliferation through an autocrine mechanism mediated by the ER [88]. Montanaro *et al.* found that ER antagonists cause upregulation of ERβ and a dose-dependent reduction in NCI-H295R cell proliferation by increasing FasL, a proapoptotic figure [88]. Recent work by Sirianni and colleagues identified that ERα plays a critical role in IGF-II- and 17β-estradiol-dependent ACC cell proliferation. They showed that a selective estrogen antagonist reduced IGFR1 protein levels and decreased IGF-II and 17β-estradiol stimulated cell proliferation [89]. They also revealed significant tumor volume reduction with estrogen antagonist treatment in a mouse xenograft model. Tumor volume decreased by 46.7% compared with tumor size at the beginning of treatment and by 56.7% compared with control mice tumors [89]. These preclinical data provide an exciting new potential treatment pathway for ACC.

1α,25-dihydroxyvitamin D_3

Several studies have shown that 1α,25-dihydroxyvitamin D_3(1α,25[OH]$_2$$D_3$) can inhibit cell growth and affect tumor invasion and angiogenesis in several different cell lines [90-92]. Pilon *et al.* looked at the ACC cell line NCI-H295R and the effect 1α,25(OH)$_2$ D_3 had on cell proliferation and steroid secretion [93]. They found a 20% reduction in cell proliferation caused by cell arrest in G1 and identified a decrease in steroid production secondary to the antiproliferative effect of 1α,25(OH)$_2$ D_3 on the cells [93]. This early preclinical study may indicate further investigation of 1α,25(OH)$_2$ D_3 as a potential new treatment option for ACC.

Current ongoing trials

The advances in molecular profiling have led to an improved understanding of ACC pathogenesis and have resulted in new clinical trials for patients with ACC. Table 1 displays the current available trials that are actively recruiting patients at the time of writing this review. Updated statuses of clinical trials for patients with ACC are available at www.clinicaltrials.gov.

Conclusion

Adrenocortical carcinoma is an aggressive tumor with limited treatment options resulting in a less than favorable outcome. Standard systemic therapies provide benefit to a small fraction of patients and the toxicities make these treatments less appealing to patients. Recent advances in the molecular biology of ACC have provided options for potential new targeted therapies. However, to date the clinical data are underwhelming. As we continue to discover the molecular mechanisms involved with ACC pathogenesis, new therapies and pathways are actively being investigated to provide hope for a new era of treatment in ACC.

Future perspective

The aggressiveness of ACC, limited therapeutic options and poor patient outcomes have compelled the medical research community to investigate the molecular biology of ACC to allow for better insight into the tumorigenesis of this disease. As our knowledge and understanding of ACC molecular pathways increase so will the number of potential therapeutic targets that are specific to the tumors, thus leading to more clinical trials and potentially a personalized approach to each individual tumor biology. Such an approach can result in higher efficacy and reduced toxicity. In addition, there is an urgent need to understand the role of adjuvant therapy in localized resected ACC. The results of the ADUIVO trial will hopefully provide guidance on this topic. We are hopeful that the drive for better understanding of ACC pathogenesis will lead to the development of new effective therapeutic treatments, particularly targeted therapy, better diagnostic and prognostic markers, and an overall improvement in patient outcomes.

Executive summary

- Mitotane, as a single agent or in combination with other cytotoxic drugs, is the current standard treatment for advanced adrenocortical carcinoma (ACC).

Response rates are dismal at approximately 30%. The FIRM-ACT trial revealed that mitotane plus etoposide, doxorubicin and cisplatin had an improvement in progression-free survival (PFS) compared with mitotane plus streptozosin.

- The role of mitotane in the adjuvant setting is controversial but the pending results of the ADIUVO trial may help clarify the role of mitotane in earlier stage disease.
- Gene expression profiling has improved our understanding of the oncogenesis of ACC and helped identify potential new targets for treatment.
- Several pathways have been identified in the tumorigenesis of ACC. IGF-2, mTOR, EGFR and VEGF are overexpressed in ACC. *In vitro* and *in vivo* studies have been preformed to identify potential targeted therapies for ACC.
- β-catenin, steroidogenic factor-1, PPARγ and estrogen receptors have all been identified as potential markers for ACC tumorgenesis. Preclinical studies are currently ongoing to identify and validate new targeted drug treatments for ACC.

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Table 1

Clinical trials that are actively recruiting patients with adrenocortical carcinoma.

Clinical trial	NCT number	Primary outcome
Phase II Trial of Surgical Resection and Heated Intraperitoneal Peritoneal Chemotherapy (HIPEC) for Adrenocortical Carcinoma	NCT01833832	Intraperitoneal progressionfree survival
Phase I Study of the Safety and Tolerability of ATR-101 in Adrenocortical Carcinoma	NCT01898715	Determine dose-limiting toxicity and maximum-tolerated dose
A Phase I/II Trial of IL-13-PE in Patients With Treatment Refractory Malignancies With a Focus on Metastatic and Locally Advanced Adrenocortical Carcinoma	NCT01832974	Maximum-tolerated dose and objective response in Phase I, progression free survival in Phase II
A Phase I/II Dose Escalation Study to Determine the Safety, Pharmacokinetics, and Pharmacodynamics of Intravenous TKM-080301 in Patients With Advanced Solid Tumors	NCT01262235	Determine dose-limiting toxicity, maximum-tolerated dose and antitumor activity
Efficacy of Adjuvant Mitotane Treatment in Prolonging Recurrence-free Survival in Patients With Adrenocortical Carcinoma at Low-intermediate Risk of Recurrence (ADIUVO trial)†	NCT00777244	Disease-free survival

†European trial – no sites available in the USA.