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Current and evolving treatment options in adrenocortical carcinoma: where do we stand and where do we want to go?

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Abstract

Adrenocortical carcinoma (ACC) is not only a rare and heterogeneous disease but also one of the most aggressive endocrine tumors. Despite significant advances in the last decade, its pathogenesis is still only incompletely understood and overall therapeutic means are unsatisfactory. Herein, we provide our personal view of the currently available treatment options and suggest the following research efforts that we consider timely and necessary to improve therapy: i) for better outcome in localized ACCs, surgery should be restricted to experienced centers, which should then collaborate closely to address the key surgical questions (e.g. best approach and extent of surgery) in a multicenter manner. ii) For the development of better systemic therapies, it is crucial to elucidate the exact molecular mechanisms of action of mitotane. iii) A prospective trial is needed to address the role of cytotoxic drugs in the adjuvant setting in aggressive ACCs (e.g. mitotane vs mitotane + cisplatin). iv) For metastatic ACCs, new regimens should be investigated as first-line therapy. v) Several other issues (e.g. the role of radiotherapy and salvage therapies) might be answered – at least in a first step – by large retrospective multicenter studies. In conclusion, although it is unrealistic to expect that the majority of ACCs can be cured within the next decade, international collaborative efforts (including multiple translational and clinical studies) should allow significant improvement of clinical outcome of this disease. To this end, it might be reasonable to expand the European Network for the Study of Adrenal Tumors (ENSAT) to a truly worldwide international network – INSAT.

Introduction

Adrenocortical carcinoma (ACC) derives from cells of the adrenal cortex and is a very aggressive endocrine malignancy. Within the last decade alone, the world has seen a boom of publications in the field of ACCs with the appearance of nearly as many articles listed in PubMed as in the preceding 50 years (n=1132 between 2004 and

Invited Author’s profile

Prof. M Fassnacht is Head of the Department of Endocrinology and Diabetes, University of Würzburg. Research in his laboratory aims at a better understanding of the pathogenesis of adrenal tumors and new treatment strategies for adrenocortical carcinoma. He has run several clinical trials for different endocrine tumors, including the first randomized trial for adrenocortical carcinoma, FIRM-ACT. He is currently the head of the adrenocortical carcinoma working group of the European Network for the Study of Adrenal Tumors (ENSAT).
2014 vs \( n = 1298 \) between 1950 and 2003). However, a breakthrough in the treatment of patients with this often fatal disease was not achieved. Despite numerous collaborative efforts including several international networks, such as the European Network for the Study of Adrenal Tumors (ENSAT), the prognosis of patients is still poor – and certainly worse than we expected 10 years ago. Thus, new treatment strategies are urgently needed. In the last few years, different groups published comprehensive reviews on the best management of ACCs (1, 2, 3, 4, 5, 6). Therefore, the aim of this article is to provide a personal tinted overview of recent advances in the treatment of ACCs and to suggest some next steps in clinical research, but also to speculate about, future therapeutical approaches.

**Current treatment concepts and suggestions for improvement**

Despite presumably best care, the relapse rate in ACCs is high and overall survival remains generally poor (5-year survival ranging from 81% for ENSAT tumor stage 1 to 13% for ENSAT tumor stage 4 (7)), with a remarkable individual variation (6). A first step to improve clinical outcome is to optimize current treatment options (Table 1). Herein, we will describe our suggestions for the upcoming years.

**Surgery**

For most patients, surgery is the first-line treatment and still the only modality that comes with a significant rate of cure. However, even a substantial number of patients with localized disease experience recurrent disease. Although we believe that relapse rates of 80% were overestimated through selection bias in earlier series (8, 9, 10, 11), more recent studies still conclude that 30–50% of radically resected patients develop disease recurrence (12). Therefore, we wonder how surgery can be improved to yield better results (Table 1).

Currently, most patients undergo surgery in hospitals with limited experience in adrenalectomy. For instance, in the USA, most adrenalectomies are performed in centers with a volume of less than six adrenal surgeries per year (13). Our own data from Germany support this view.

Table 1

<table>
<thead>
<tr>
<th>Presumed/potential obstacles</th>
<th>Suggestion for improvement</th>
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<tbody>
<tr>
<td>To reduce the high recurrence rate in localized disease</td>
<td>Restriction of surgery for suspected ACCs to centers that performed at least 20 adrenalectomies per year and have established multidisciplinary structures for ACC treatment</td>
</tr>
<tr>
<td>Most surgeries for ACCs are performed in low-volume hospitals with little experience in ACCs</td>
<td>Clinical trial or prospective data collection to identify the best approach (laparoscopy vs open surgery) and extent of surgery</td>
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<tr>
<td>There are no generally accepted standards for surgery available</td>
<td>Multicenter data collection from at least 100 patients plus 200 matched controls</td>
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<tr>
<td>The role of adjuvant radiotherapy is ill-defined</td>
<td>Randomized clinical trial (e.g. mitotane vs mitotane plus three cycles of cisplatin, 90 mg/m²)</td>
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<tr>
<td>Adjuvant mitotane is insufficient in patients with aggressive ACCs</td>
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To improve the poor clinical outcome in patients with advanced disease

| Mitotane acts too slowly                                                                     | Improvement of mitotane pharmacokinetics by improving posology or metabolic boosting     |
| EDP–M is effective only in a subset of patients and might be an overtreatment in less aggressive disease | Non-inferiority trial, EDP–M vs P–M (e.g. with cisplatin 90 mg/m²)                          |
| Stratification score to identify patients with less aggressive disease who are suitable for mitotane monotherapy or experimental approaches |                                                                                           |
| Individualization of treatment by establishment and validation of predictors of response (e.g. ERCC1 for platinum compound therapy) |                                                                                           |
| Retrospective multicenter studies (100 patients per regimen) to investigate the efficacy of currently used regimens (e.g. gemcitabine + capcitabine) |                                                                                           |
| Multicenter phase II trials using ‘targeted therapies’ in first-line treatment (e.g. sunitinib vs mitotane) |                                                                                           |
| Identification of markers that predict response to IGF1R inhibitors                          |                                                                                           |
| Evaluation of combination therapies with IGF1R inhibitors                                     |                                                                                           |

EDP, etoposide, doxorubicin, cisplatin. M, mitotane. ERCC1, excision repair cross-complementation group 1; IGF1R, insulin-like growth factor 1 receptor.
In the last decade, 472 adrenalectomies have been documented in the German ACC registry. These procedures have been performed in 234 different surgical and urological departments and only six centers executed more than ten primary surgeries within this time frame. Recent data from Italy and The Netherlands (14, 15) suggest that surgical volume has an impact on clinical outcome of patients with ACCs. Although we cannot prove that this hypothesis is true, it is tempting to believe that it does. Therefore, we strongly suggest that surgery for suspected ACCs should be limited to specialized centers that perform >20 adrenalectomies per year and have established multidisciplinary structures for ACC treatment.

Another problem is the lack of standardization in surgery of ACC. From our point of view, there are at least three key unanswered questions: i) is minimally invasive adrenalectomy of benefit or harm in patients with localized ACCs? ii) Do all patients with suspected ACCs require loco-regional lymph node dissection? If so, to what extent? iii) Which patients with metastasized ACCs benefit from surgery? As to the first question, several retrospective studies have now been published (16, 17, 18, 19, 20, 21, 22, 23, 24), but there is no conclusive answer to date. As to the other two questions, the available literature is even scarcer (9, 25, 26, 27). Therefore, we urgently need prospective trials addressing these issues. However, sound clinical studies in this context are very demanding and it is unlikely that they will be performed in the near future. Thus, data should prospectively be collected in consecutive series to provide more convincing evidence. In the meantime, we currently comply with the following approach: for tumors smaller than 8 cm and without evidence of local invasion, laparoscopic surgery including loco-regional lymph node dissection in an expert center seems to be acceptable and may even be preferable in selected cases. However, before surgery, we inform our patients that this procedure is still not standard of care and minimally invasive surgery will only be performed if the patient explicitly agrees with this approach. In all other patients with localized ACCs, open surgery along with lymph node dissection is the treatment of choice. For metastatic disease, we rarely see an indication for debulking surgery with the exception of patients with clinically relevant hormone excess. However, we are wondering if a reduction of tumor burden would lead to an improved response to systemic therapy (especially in patients in good clinical condition). In case of recurrent disease, we recommend surgery only for patients with a disease-free interval of more than 12 months and in whom a complete resection is feasible (25). By contrast, we advocate against surgery if the time between surgery and recurrence is <6 months, because systemic therapy is probably more efficient in this context and would be delayed by surgery. Finally, we consider surgery in patients with advanced disease if systemic therapy was able to control the disease for at least 4–6 months and a radical surgical approach seems to be feasible.

Mitotane

The paramount importance of mitotane in the treatment of ACCs both in an adjuvant setting and as a palliative treatment has been intensively discussed in recent reviews (5, 28, 29). Mitotane is well established as the backbone of treatment in advanced ACCs both in monotherapy and in combination with cytotoxic drugs (6, 29, 30). Therefore, we will only shortly summarize its current use and focus more on the scientific challenges and clinical uncertainties linked with this drug.

Although not generally accepted, we agree with many other centers that perceive a benefit in recurrence-free and overall survival from adjuvant mitotane after complete ACC resection (31). The prospective ADIUVO trial (comparing adjuvant mitotane treatment with observation only) should provide the first answer in the upcoming years (http://www.adiuvo-trial.org). We strongly encourage clinicians to include patients with a presumably low risk of recurrence in this international trial headed by Massimo Terzolo.

It appears that mitotane hurts the Achilles’ heel of ACCs. However, the major obstacle when it comes to improving mitotane treatment or finding better alternatives lies in the fact that the exact mechanism of action is still unknown – despite its clinical use for more than 60 years. Coming from a physiological perspective, adrenocortical cells are characterized by a high turnover of cholesterol into steroid hormones. For this, a highly activated system of redox reactions is required. Hence mitochondria and endoplasmic reticulum might be susceptible targets and implicated in the mode of action of mitotane (32).

From a clinical point of view, it appears that mitotane acts relatively specifically on adrenocortical tissue rendering mitotane a kind of a ‘targeted therapy’. As nicely elaborated by Huang & Fojo (33), it is still unclear whether mitotane actually ‘kills’ adrenocortical cells (i.e. being adrenotoxic), or just hinders their growth and proliferation (i.e. acting as adrenostatic). The experience with mitotane monotherapy in patients with advanced disease suggests a true adrenotoxic effect, because objective response rates of some 25% have been reported (29, 34).
However, in the long run, adrenal function usually recovers after stopping mitotane, suggesting an adrenostatic effect more than a true toxic effect – at least on normal adrenocortical cells.

It is currently supposed that reactive metabolites formed by oxidation of mitotane covalently bind to mitochondrial proteins that – by unclear intermediate steps – lead to inhibition of the mitochondrial respiratory chain and several enzymes in the adrenocortical steroidogenesis pathway (35, 36). This was confirmed to some extent in cell culture suggesting that down-regulation of the mitochondrial respiratory chain might be involved in the cytotoxic effect of the drug (37, 38). We personally have some doubts if the covalent binding of a mitotane intermediate to mitochondrial proteins is actually causative of decreased steroid synthesis and cell death in ACCs as i) in the original report, protein adducts have been mainly found in non-human adrenocortical tissue and only weakly in NCI-H295 cells, ii) these presumed adducts have never been identified, and iii) alterations of the respiratory chain also occur during apoptosis which may be triggered by completely separate pathways. Hence, these adducts may be an epiphenomenon caused through the high reactivity of the chlorinated compound mitotane and high oxidative activity of adrenocortical cells. It is a relevant obstacle to these and other investigations that NCI-H295 cells are the only reliable model system for ACCs and alternatives are unavailable with the exception of SW13 cells, which is most likely an even less suitable cell line.

Just like with the mechanism of action, the pharmacokinetic data are alarmingly limited (39, 40, 41). Thus, it has become clear by thorough investigation of a fortuitous finding, namely reduced plasma concentrations of sunitinib and its active metabolite during concomitant mitotane treatment (42), that mitotane is one of the strongest inducers of CYP3A4 – the major drug-metabolizing enzyme in humans leading to multiple drug interactions (for review see (43)). Till date, it is unclear whether mitotane itself is metabolized by CYP3A4 and which other P450 enzymes are altered in their activity, although there is first evidence that CYP2B6 might be involved (44). However, it appears to us as an appealing option to inhibit hepatic mitotane metabolism in a manner similar to the current clinical practice during treatment for HIV where protease inhibitors are boosted through concomitant application of ritonavir, a strong CYP3A4 inhibitor (45).

Another important step forward to improve mitotane treatment would be the establishment of markers that predict drug response. Earlier studies suggested that expression of the gene encoding ribonucleotide reductase large subunit (RRM1) (46) or CYP2W1 (47) may be of importance, but more and larger studies are required to confirm this.

In conclusion, a better understanding of mitotane is not only required to allow prediction of the individual response but also a prerequisite for the development of less toxic compounds. However, we clearly have the vision that in the future we can omit administering ‘old-fashioned’ mitotane to our patients.

Radiotherapy and other locally ablative modalities

In general, radiotherapy has significantly advanced in recent years, but the role of radiotherapy in the management of ACCs is still a matter of debate. Almost 10 years ago, we performed a first, small retrospective study examining external beam radiotherapy of the tumor bed in an adjuvant setting (48). In this study, 14 patients with radiotherapy were compared with 14 matched controls without radiotherapy, and we could demonstrate significant reduction of local recurrences. In the following years, two similar studies came to divergent results. The series from the Ann Arbor group also found a reduced risk of local recurrence (49), whereas a study from the MD Anderson Cancer Center reported no benefit of adjuvant radiotherapy (50). Of note, none of these studies could show an improvement in disease-free or overall survival. Thus, we are not convinced that a randomized trial is justified yet and would prefer to see a large multicenter effort to collect data from at least 100 patients with adjuvant radiotherapy. Results should then be compared with matched controls to define the subgroup of patients who might benefit from this procedure.

Concerning the use of radiotherapy in advanced ACCs, the few data available indicate some palliative efficacy by reducing symptoms from painful bone metastasis or brain and bulky abdominal tumors (8, 49, 51, 52, 53, 54, 55, 56).

Therefore, radiotherapy is an important tool in the multidisciplinary management of a patient, but we would not see it at the forefront of urgent scientific questions.

Similarly, the role of other ablative measures such as radiofrequency ablation and chemoembolization is ill-defined, but there is evidence that a subgroup of patients will benefit from these modalities, probably and especially those patients with liver metastases and less aggressive tumors. However, the suggestions proposed by the group of Eric Baudin (2) need to be confirmed in large cohort studies.
Cytotoxic drugs

The results of the FIRM-ACT study – which is still the only published randomized trial in ACCs – clearly established the combination of etoposide, doxorubicin, and cisplatin plus mitotane (EDP–M) as a standard cytotoxic therapy for advanced ACCs (57). However, with a median progression-free survival of only 5.0 months and an overall survival of 14.8 months, it is obvious that better treatment options are needed. The poor outcome coupled with the fact that EDP–M was similarly effective in the second-line treatment as it was in the first-line treatment brings us to the following conclusions (5): i) for some selected patients with presumably less aggressive disease (e.g. slowly progressing tumor growth, only two involved organs, and long disease-free interval after initial surgery), mitotane monotherapy might be justified as first-line treatment. ii) The same patients, however, might also be good candidates for experimental therapies up front, as efficacy of several targeted therapies is most likely diminished by mitotane due to the increased drug metabolism (58). Thus, from our point of view, prior or co-treatment with mitotane is almost a contraindication to test drugs metabolized by CYP3A4 in ACCs if dose adjustment based on therapeutic drug monitoring is not performed.

Till date, there is no other drug regimen that holds realistic promise to be superior to EDP–M. Therefore, until evidence for improved therapeutic options becomes available, we have to deal with our current drug arsenal. In this context, the following questions seem to be most relevant for the near future: i) do we really need the cocktail of four drugs to make EDP–M efficient? This question is further fueled by the potential drug interaction of mitotane with these cytotoxic drugs (43). However, only a demanding prospective non-inferiority trial can answer this question. ii) What is the second best cytotoxic drug regimen (e.g. for patients failing EDP–M)? Again a comparative trial would be ideal; however, large retrospective studies might also provide some clues. For now, gemcitabine + capecitabine (59), thalidomide (60), or metronomic cytotoxic regimens (61) might be reasonable schemes to be evaluated on a larger scale. iii) Is there a role for cytotoxic drugs in the adjuvant setting? Till date, no evidence has been published for such an approach. Nevertheless, we presume that for a subset of patients with a high risk, a platinum-based therapy in addition to mitotane could be beneficial (e.g. three cycles of 90 mg/m² cisplatin in patients with Ki67 > 30% and a large tumor thrombus in the vena cava). In a very recent approach, the group from Felix Beuschlein provided evidence that nanotechnologically modified cytotoxic drugs, especially liposomal doxorubicin and liposomal cisplatin, were more effective in a mouse xenograft model for ACCs than the plain drugs (62).

An additional concept for improving the outcome of classical cytotoxic therapy might be individualized treatment. However, to facilitate such a concept, predictors of response have to be established and validated. Few attempts by us and others have been made (46, 63, 64), but the data are not yet conclusive and the series are too small for final conclusions.

Molecular targeted therapies

As extensively discussed elsewhere (5, 29, 65), the available results of targeted therapies, such as antibodies or tyrosine kinase inhibitors (TKIs), are largely disappointing. There are potential explanations for the poor outcome of these new drugs: heavily pretreated patients with refractory tumors, severe drug interaction due to mitotane pre- or co-treatment, insufficiency of a monotherapy of these drugs, or these drugs just did not attack the ‘right target’ (Table 1).

In the last few years, several studies were launched that investigated drugs targeting the insulin-like growth factor 1 receptor (IGF1R). This approach was associated with great hopes, because IGF2 was shown to be the most over-expressed gene in ACCs by far, and it was thought that this pathway was one of its key drivers (66). However, we had to learn that IGF1R inhibitors (either antibodies or kinase inhibitors) are obviously not the ‘magic bullet’. In fact, in most of these trials, there was only a subset of patients who benefited from these drugs (67, 68), but overall the response rates (and particularly the impact on progression-free and overall survival) were poor. It appears that targeting either IGF1R or mTOR – one of the downstream targets of IGF1R (69) – probably leads to compensatory activation of other pathways. Nevertheless, the fact that there are some remarkable responses to IGF1R inhibitors (e.g. we are taking care of two patients who have experienced an ongoing impressive partial response for at least 40 months after treatment initiation) makes us believe that the concept of IGF1R inhibition should not be finally abandoned.

Therefore, we face the challenge of establishing markers that identify those few responders. In other tumor entities (e.g. lung cancer), it is by now well accepted to screen for small and distinct subgroups that may benefit from specific drugs (e.g. ALK inhibitors). Without doubt,
only an international study can meet this challenge in a rare disease such as ACCs.

Targeting of tumor vasculature has also attracted attention in ACC treatment as we and others have detected high expression of vascular endothelial growth factor (VEGF (VEGFA)) and its receptor VEGFR2 (KDR) in many ACC specimens (43, 70, 71, 72). Among the VEGF-targeting drugs (58, 73, 74, 75), the multi-TKI sunitinib has demonstrated modest anti-tumor effects in a phase II clinical trial. Of the 35 patients analyzed per protocol, five patients (14%) experienced stable disease, but no objective tumor response was observed (58). However, this trial has taught us another lesson, confirming the negative drug interaction between mitotane and sunitinib. Taken together, some part of the inefficacy of TKI in ACCs may be attributed to drug interaction with mitotane, especially given the very long half-life of mitotane (76, 77). Thus, as already mentioned, a first-line trial of a TKI such as sunitinib vs mitotane seems to be justified and is currently in the phase of conception.

**Evolving and possible future treatment concepts**

Treatment with specific radioactive isotopes is an intriguing therapeutic concept that is well established for other endocrine tumors. In the last decade, our group in Würzburg (spearheaded by Stefanie Hahner, Bruno Allolio, and Andreas Schirbel) has developed a radio-nuclide therapy based on [131I]iodometomidate (IMTO) (78). So far, 11 patients with advanced ACCs have been treated with [131I]IMTO on a compassionate-use basis. In one patient, a decrease in tumor burden of some 50% has been found, which lasted for more than 26 months (Fig. 1). Five additional patients experienced stable disease, in three of whom it lasted for at least 10 months (79). Unfortunately, technical and regulatory obstacles hampered further progress, but we just re-launched the program and intend to prove if the concept continues to be promising (Table 2).

By searching in the ‘ClinicalTrials.gov’ database, we identified several trials that are currently open for ACCs, but all of them are early-phase trials (e.g. ATR-101, NCT01898715). In countries without open clinical trials, patients with refractory ACCs should be offered inclusion in early clinical trials for solid tumors that are not restricted in terms of tumor histology (‘all comers’) in order to detect any substance with clinical potential.

A literature search for *in vitro* data in ACC cell culture and animal models yielded the following concepts that merit further investigation from our point of view: dual PI3 kinase/mTOR inhibition by NVP-BEZ235 (80), heat shock protein 90 (HSP90 (HSP90AA1)) (81) inhibitors, proteasome inhibitors such as bortezomib (82), and inhibitors of steroidogenic factor 1 (SF1) (83). Especially, the latter approach seems to be particularly interesting to...
us, because virtually all ACCs express this nuclear receptor (84, 85), which makes us believe that SF1 is essential for ACC cells. However, for all of these drugs, the road from first in vitro data to patients is still long and a rapid introduction into clinical practice is unlikely (Table 2).

Table 2  New concepts for future studies on adrenocortical carcinomas (ACCs).

<table>
<thead>
<tr>
<th>Drug/concept</th>
<th>Rationale</th>
<th>Limitation</th>
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<tbody>
<tr>
<td>'Improved mitotane’</td>
<td>Elucidation of the mechanism of action of mitotane should pave the way toward the development of new ACC-specific drugs</td>
<td>The current knowledge about the molecular mechanisms of mitotane is very limited</td>
</tr>
<tr>
<td>Combination of IGF1R inhibitor with other drugs [131I]iodometomidate therapy</td>
<td>IGF1R inhibition probably leads to compensatory activation of other intracellular pathways</td>
<td>Reasonable combination partners (especially in the context of ACCs) are not yet identified</td>
</tr>
<tr>
<td>SF1 inhibitors</td>
<td>SF1 is expressed in virtually all ACCs and SF1 inhibitors are effective in vitro (83)</td>
<td>Synthesis of [131I]iodometomidate is not well established</td>
</tr>
<tr>
<td>Nanotechnologically modified cytotoxic drugs</td>
<td>Adrenocortical cells are particularly susceptible to liposomal drugs (62)</td>
<td>There is not yet any drug that can be tested in humans</td>
</tr>
<tr>
<td>Individualized therapy based on identification of driver mutations</td>
<td>Experience in other tumor entities</td>
<td>Only liposomal doxorubicin is clinically available</td>
</tr>
</tbody>
</table>

IGF1R, insulin-like growth factor 1 receptor; SF1, steroidogenic factor 1.

Figure 2 summarizes our personal view on interesting cellular targets that might be worthwhile to be further investigated.

Outlook beyond the next decade

All the efforts mentioned above will hopefully lead to a stepwise improvement of ACC patient care. However, they will most likely not result in the required breakthrough to defeat this nasty disease. To actually reach the desired quantum leap, we need a better understanding of the pathogenesis of adrenocortical tumors and have to identify the true ‘drivers’ of the disease. In recent years, significant advances have been achieved in this field, for instance by new molecular techniques (86, 87, 88, 89, 90, 91, 92). Although these results gave insight into the heterogeneity of the disease and may help to define patients with different prognosis, these studies did not yet improve clinical care.

Currently, two international consortia (ENSAT led by Jerome Bertherat and The Cancer Genomic Atlas group led by Tom Giordano) try to solve the riddle of ACCs using exome sequencing and integration of different ‘omic-studies’. The results of these important studies are expected in the near future and might guide us toward better diagnostic, prognostic, and therapeutic approaches. However, in contrast to adrenal adenomas (93, 94), it is very unlikely that we will identify just one or few key driver mutations, because an ACC is a much more heterogeneous and de-differentiated disease. Furthermore, the current techniques might not be sufficient to identify the driver beyond classical mutation and additional modern tools (e.g. whole genome sequencing) could be required. Another interesting approach might be the identification of a (relatively) specific cell surface marker of ACCs. For instance, such a marker would allow to target
tumor cells by immunotherapeutic measures as currently successfully demonstrated for other tumor entities (95).

In conclusion, it is unrealistic to expect miracles within the next few years, but we are convinced that these translational approaches will give us a vision of how to pave the path for better treatment of ACC patients in the future.

Declaration of interest
M Fassnacht participated as an investigator in clinical trials on adrenocortical carcinomas sponsored by HRA Pharma and Astellas Pharma respectively. In addition, he has received a lecture honorarium from HRA Pharma. The other authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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