

Review

# Medical management of adrenocortical carcinoma: Current recommendations, new therapeutic options and future perspectives

## *Prise en charge médicale du corticosurrénalome malin: recommandations actuelles, nouvelles options thérapeutiques et perspectives*

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### ARTICLE INFO

#### Keywords:

Adrenal  
Cancer  
Mitotane  
Chemotherapy  
Immunotherapy

### ABSTRACT

Adrenocortical carcinoma is a rare malignant tumor of poor prognosis, frequently requiring additional treatments after initial surgery. Due to its adrenolytic action, mitotane has become the first-line medical treatment in patients with aggressive adrenocortical carcinoma. Over the last 2 years, apart from the classical chemotherapy based on etoposide and platinum salts, several studies reported the use of drugs such as temozolomide, tyrosine kinase inhibitors or immunotherapy, with more or less convincing results. The aim of this review is to give further insights in the use of these drugs, and to describe potential therapeutic perspectives based on recent pangenomic studies, for the future management of these still difficult to treat tumors.

### RÉSUMÉ

Le corticosurrénalome malin est une tumeur rare, de mauvais pronostic, nécessitant fréquemment le recours à des traitements médicamenteux après la chirurgie initiale. Depuis de nombreuses années, le mitotane est le traitement de 1<sup>re</sup> ligne des corticosurrénalomes agressifs, du fait de ses propriétés adrénolytiques. Cependant, ce traitement est souvent insuffisant et associé à une chimiothérapie de type Etoposide/Platine. Au cours des 2 dernières années, plusieurs études ont rapporté l'efficacité plus ou moins probante de nouvelles molécules telles que le temozolomide, les inhibiteurs tyrosine kinase ou l'immunothérapie. L'objectif de cette revue est de préciser les résultats de ces différentes études, et d'apporter quelques données de perspectives basées sur les études pangénomiques, dans l'objectif de mieux appréhender ce que pourrait être la prise en charge de ces tumeurs dans les années à venir.

#### Mots clés :

Surrénales  
Cancer  
Mitotane  
Chimiothérapie  
Immunothérapie

## 1. Introduction

Adrenocortical carcinoma (ACC) is a rare malignant tumor with an annual incidence of between 0.7 to 2 cases per million population per year [1,2]. The disease can appear at any

age, with a peak in childhood and a plateau between 40 and 60 years old, with women being substantially more frequently affected than men (60% vs. 40%) [3]. Around 55% of patients present with symptoms linked to adrenocortical hypersecretion (in general hypercortisolism ± combined with hyperandrogenism), while 30–40% of patients have symptoms related to tumor volume, and the other 10% are discovered fortuitously [4].

ACC prognosis is mixed, with a 5-year survival rate that varies between 80% for patients with localised disease to 15% in patients presenting with more advanced disease (stage III–IV), according to

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the staging proposed by the European Network for the Study of Adrenal Tumors (ENS@T) [5]. In addition to ENS@T stage, patient age [6], R0 status (cancer surgery by laparoscopy except in the case of contrary decision taken by expert surgical team) [7], Ki-67 index [8], as well as molecular markers [9], have proven useful when looking at prognosis in patients with an ACC. Integrative models that take into account both the clinical features of the tumor and molecular prognostic markers seem to facilitate more precise characterisation of patient prognosis [10].

Due to their rarity, the recommendations for management of ACC rely purely on data from retrospective studies, and few therapeutic options are currently available. Complete tumor resection, including peri-tumoral fat, as well as locoregional lymphadenectomy, when this is feasible, currently represents the best curative option for patients with an ACC [4]. The recurrence rates reported in the literature are quite variable, being 30–85% [11,12]. Recruitment bias and different initial modalities of treatment at the commencement of patient management likely explain the differences in data from different centers. The rarity of the disease means that patients require personalised care by a multidisciplinary team, expert in managing ACC, and that each case is discussed in a multidisciplinary meeting based on current recommendations.

This literature review will evaluate currently-used medical therapies for management of ACC and will also particularly focus on new therapies that are or will be available.

## 2. Currently recommended therapies

### 2.1. Mitotane

Mitotane is currently the only treatment that is recommended for the management of advanced ACC and its use is advocated in many centers for the treatment of patients at high risk of recurrence, that is, those with ENS@T stage III tumors (pT3-T4, N1), those who have had incomplete surgical resections, and those with Ki-67 index > 10% [4].

At the molecular level, mitotane acts via inhibition of sterol-O-acetyl transferase enzyme (SOAT-1), leading to endoplasmic reticulum stress and lysis of adrenocortical cells [13]. Mitotane is a drug with a very long half-life, high toxicity and a therapeutic window that is very narrow (between 8 and 25 mg/mL). The dose of mitotane needs to be guided by, at minimum, monthly measurements of serum levels of the drug. Due to the adrenolytic activity of mitotane, glucocorticoids (hydrocortisone) need to be administered to avoid patients suffering acute adrenal insufficiency, the dose being around 50 mg per day, though due to the enzymatic activity of mitotane, the dose may need to be as high as 80–100 mg/day. Most published studies have suggested that treatment needs to be maintained for at least 2 years (range: 2–5 years), due to the frequency of recurrence being high during this period. In view of the poor tolerance of the treatment in a significant number of patients, the duration of treatment also depends on the risk–benefit ratio, which needs to be evaluated on a case by case basis, on the basis of mitotane levels and of treatment tolerance (INCa Comete Network).

In a retrospective study that included 177 patients, the progression-free survival in the group of patients who were systematically treated with mitotane as adjuvant therapy after complete surgical resection, was significantly higher than that of non-treated patients [14].

The question of the benefit of mitotane in patients with an ACC at low to intermediate risk of recurrence (ENS@T stages 1, 2 and 3, and R0, with Ki-67 index < 10%) is currently the subject of a randomised phase III multicenter trial (ADIUVO, NCT00777244). According to several studies, the objective tumor response rate for advanced ACC

is between 13 and 31%, though these studies were of short duration [15,16].

Another randomised multicenter phase III study, coordinated by ENS@T, is currently underway. This study will evaluate the efficacy of mitotane as monotherapy compared to mitotane combined with cisplatin and etoposide, in patients who have undergone surgery for ACC and have a high risk of recurrence (ADIUVO-2, NCT03583710).

### 2.2. Cytotoxic chemotherapy

Chemotherapy, based on platinum salts, generally in combination with etoposide (doxorubicin) and mitotane (E(D)P-M), currently represents first-line treatment for advanced ACC [4]. This recommendation comes from the FIRM-ACT trial which showed greater efficacy using the E(D)P-M protocol compared to a treatment group who received streptozotocin combined with mitotane, with a progression-free survival of 5.5 versus 2.1 months [17]. Later, a phase II trial looking at the combination of cisplatin and docetaxel, as first-line chemotherapy, reported a progression-free survival of 3 months and a partial response in 21% of cases [18]. However, none of the patients in this study showed a complete response, thus this treatment modality was not retained as first-line chemotherapy.

Current recommendations for management of ACC suggest 2nd line therapies for those patients who show progression after the E(D)P-M protocol [4]. Two cytotoxic agents are suggested for 2nd line chemotherapy, streptozotocin combined with mitotane [17] and the combination of gemcitabine/capecitabine ± combination with mitotane [19]. However, even though some patients have benefited from long term tumoral control, these two modalities of 2nd line therapy have been disappointing in terms of efficacy, with the rate of objective tumoral response being < 10% and the median progression-free survival < 4 months. Local treatments (surgery, radiotherapy, chemoembolization, radiofrequency ablation. . .) should be preferred, if possible, in cases of lesions that are accessible and disease that is not already very metastatic (even before commencing systemic treatment). This has been recently suggested by a retrospective single center study that included patients with advanced/metastatic ACC. The study showed an increase in overall progression-free survival in patients who had surgical removal of residual tumor after treatment with EDP-M, compared to those who had chemotherapy alone [20].

More recently, an Italian retrospective multicenter study evaluated the efficacy of temozolomide in 28 patients with metastatic ACC who had failure of first-, second- or third-line treatment. This study showed encouraging results, with progression-free survival of 3.5 months, and an overall survival of 7.2 months [21].

Data concerning efficacy of adjuvant chemotherapy in patients with ACC are scarce. Recently, in a retrospective study including 577 patients with adrenalectomy (389 patients with adrenalectomy alone and 188 patients receiving adjuvant chemotherapy with no precise data on the type of chemotherapy, duration. . .), no correlation between adjuvant chemotherapy and overall survival was evidenced [22]. This clearly emphasizes the need to have a clear-cut protocol to determine whether patients could benefit from early chemotherapy in ACC.

## 3. New therapeutic modalities: Targeted therapies and Immunotherapy

### 3.1. Targeted therapies

#### 3.1.1. Tyrosine kinase inhibitors (TKI)

Receptor tyrosine kinases (RTK), possess a ligand binding extracellular domain, a transmembrane domain permitting signal transduction and an intracellular kinase domain that is involved in

phosphorylation of tyrosine residues of the receptor itself, and as a consequence, its activation. Activation of RTKs induces a cascade of signalling (via phosphorylation) which leads to the activation of transcription factors which regulate cell growth and differentiation. Selective tyrosine kinase inhibitors exist, as well as multi-tyrosine kinase inhibitors, which can be used as anti-cancer drugs.

**3.1.1.1. Multi-tyrosine kinase inhibitors (mTKI).** Tumoral neoangiogenesis is a well-established therapeutic target in numerous cancers. The majority of mTKIs currently in use target vascular endothelial growth factor (VEGF) and its receptor (VEGFR2), and also generally inhibit other kinases, such as those of platelet derived growth factor receptors (PDGFR), the epidermal growth factor receptor (EGFR) and fibroblast growth factor receptor (FGFR), to varying degrees. ACCs often show a clear over-expression of VEGF and of its receptor VEGFR2 [23,24], suggesting it may be beneficial to use mTKI in these patients.

Sorafenib and sunitinib have been evaluated as therapies in the management of ACC: in fact, preclinical data suggests efficacy of these two mTKIs [23,24]. However, a phase II study which included 9 patients with advanced ACC, treated with metronomic chemotherapy using sorafenib and paclitaxel, was interrupted early due to early progression of the disease in all 9 patients [25]. Additionally, in the phase II SIRAC trial, only 5 of 35 patients with ACC who showed disease progression after first-line treatment, showed stable disease at the first evaluation 12 weeks after treatment initiation, and the median disease-free survival was 2.8 months [26].

Cabozantinib is an inhibitor of c-MET, VEGFR2, AXL and RET and has been recommended for use in several solid cancers. A multicenter study, including 16 patients with ACC, has recently been published [27]. This study showed an objective tumoral response in 3 patients as well as progression free survival of more than 4 months in 8 patients, suggesting significant clinical efficacy.

Currently, two phase II trials of cabozantinib in patients with ACC are in the process of patient recruitment in Europe (NCT03612232) and the United States (NCT03370718).

**3.1.1.2. Selective tyrosine kinase inhibitors (TKI).** It has been shown that dysregulation of the FGF signalling pathway is associated with tumor development as well as tumor progression. Amplification of the FGFR1 gene, shown using comparative genomic hybridization, has been described in 10.7% of patients with ENS@T stage III-IV ACC [28]. In addition, over-expression of mRNA for both FGFR2 and FGFR4 has been demonstrated in patients with ACC compared to patients with adrenocortical adenomas [29].

To date, only deranzantinib (ARQ087), a pan-FGFR inhibitor has been evaluated in a phase I trial on 4 patients with ACC. Of these 4 patients, 2 presented with stable disease of over one year [30].

Regarding the EGF signalling pathway, over-expression of membrane EGFR has been reported in 36% of ACC [31], and a reduction in cell viability was observed in primary cultures of ACC cells after inhibition of the EGFR pathway [32]. However, neither of the two TKIs that are specific for EGFR (erlotinib and gefitinib) showed any clinical benefit in patients with advanced ACC [33].

### 3.1.2. Insulin-like growth factor (IGF) pathway inhibitors

The IGF signalling pathway plays a major role in the regulation of various adrenal functions and is one of the signalling pathways that is most frequently altered in ACC [34]. IGF-2, IGF-1 receptor (IGF-1R) as well as the insulin receptor (IR), are frequently over-expressed in ACC [35], leading to an autocrine/paracrine regulatory loop in which IGF-2, by its action of stimulating IGF-1R and IR which in turn activate the IGF signalling pathway, stimulates cell proliferation, motility and survival [34].

NVP-AEW541, a selective inhibitor of IGF-1R and cixutumumab, a monoclonal antibody directed against IGF-1R, reduce the prolifer-

ation of the NCI-H295R cell line in vitro, and equally in xenografted mouse models [36,37]. However, a randomised phase III trial comparing linsitinib, a specific IGF-1R and IR inhibitor, to placebo showed no efficacy in improving progression-free survival nor on overall survival in ACC [38].

Interestingly, metformin, which is widely used in current clinical practice in the management of type 2 diabetes, interacts with the IGF-1R signalling pathway and can also have a direct anti-tumoral effect. Specifically, one study has shown an anti-proliferative effect on ACC cell lines (NCI-H295R) in vitro and in vivo in mouse xenograft models [39]. However, to date, clinical data evaluating the efficacy of metformin in management of ACC has not been reported.

### 3.1.3. Mammalian target of rapamycin (mTOR) signalling pathway

Dysregulation of the mTOR signalling pathway has been reported in patients with ACC and the use of mTOR inhibitors (sirolimus, everolimus and temsirolimus), alone or in combination with mitotane, has shown anti-proliferative effects, both in vitro and in vivo [35].

However, only few studies have evaluated the clinical efficacy of mTOR inhibitors in ACC, and these showed no benefit [40,41].

### 3.1.4. Sterol-O-acetyltransferase (SOAT1) inhibitors

Nevanimib (ATR-101) is a new SOAT1 inhibitor, which is adrenal specific. This drug has been shown, in a preclinical study, to inhibit adrenocortical steroidogenesis at low doses and to cause adrenolysis at high doses. Nevanimib has been evaluated in the setting of a phase I study including 63 patients with metastatic ACC. No patients showed either a complete or partial response. Twenty-seven percent of patients who had imaging at 2 months showed stable disease, and 4 patients showed stable disease at > 4 months [42].

## 3.2. Immunotherapy

Preclinical data on the benefit of the use of immunotherapy in management of ACC is scarce. In other types of cancer, three principal markers of response to treatment are used, these being expression of PD-1 and PD-L1, microsatellite instability (MSI) and somatic mutations. Here, we present the few trials that have evaluated the efficacy of immunotherapy in ACC.

### 3.2.1. PD-1 antagonists

The use of pembrolizumab, a programmed death-1 (PD-1) antagonist, is approved by the Federal Drug Agency (FDA) for the treatment of tumors presenting with MSI, independent of their histological profile. This approval is based on therapeutic trials that reported an objective response rate of around 40% in this patient population [43].

Recently, a phase 2 study (NCT02673333) evaluated the clinical efficacy of pembrolizumab (200 mg every three weeks) in 39 patients with advanced ACC, independent of their previous treatment [44]. The objective response rate on pembrolizumab was 23% and the disease control rate was 52%, median progression-free survival was 2.1 months and the median overall survival was 24.9 months. The expression of PD-1 and presence of MSI were not correlated to the objective response rate.

A second phase 2 multicenter single-arm study (NCT02720484) of 10 patients with metastatic ACC treated with nivolumab, gave disappointing results with a median progression-free survival of 1.8 months [45].

Additionally, a recent retrospective multicenter study evaluated the efficacy of a combination of pembrolizumab/lenvatinib and showed encouraging results, notably with a median progression-free survival of 5.5 months [46]. Evaluating therapeutic approaches

that use a combination of drugs may be of interest, potentially allowing these aggressive tumors to be controlled through treatment that targets several pathways simultaneously.

### 3.2.2. PD-L1 antagonists

A phase 1b study (NCT01772004) has evaluated the efficacy of avelumab in 50 patients with metastatic ACC. The objective response rate was 6%, with a median progression-free survival of 2.6 months and a median overall survival of 10.6 months. Twelve tumors showed over-expression of PD-L1 while 30 tumors did not over-express PD-L1, with the objective tumoral response rates being 16.7% vs. 3.3%, respectively [47].

The modest results observed with immunotherapy may be linked, in part, to an immunodepletion in these patients, possibly related to the local production of glucocorticoids by the tumor. Thus, the use of an adjuvant therapy aimed at reducing the local production of glucocorticoids might improve the response of ACC to immunotherapy [48].

## 4. Perspectives: future molecular targets

Recent pan-genomic approaches have led to the identification of genetic alterations in ACC, which could represent potential therapeutic targets of choice, but might also allow better characterization of the aggressiveness of some tumors whose prognosis is unclear at diagnosis (when defined by classical markers such as Ki-67 and ENS@T stage) [9,28,49]. These data are summarised in comprehensive reviews by Crona and Beuschlein and Altieri et al. [50,51]. Here, we will concentrate on the genes that have aroused the most interest and comprehensively describe their *in vitro*, preclinical and clinical data and their potential impact in future management of ACC.

### 4.1. Inhibitors of the Wnt/ $\beta$ catenin signalling pathway

The Wnt/ $\beta$ catenin signalling pathway plays an integral role in the development of numerous organs, notably the adrenal gland. Somatic mutations that are activating the CTNNB1 gene, which codes for  $\beta$ catenin (p.S45B) were found in 40% of ACC cases [9]. Concomitant appearance of alterations in the Wnt pathway and inactivation of TP53, induced in a transgenic mouse model, resulted in adrenocortical carcinomas in the mice that were particularly aggressive in terms of metastasis, suggesting the potential interest of molecular targeting of these two pathways (Wnt/ $\beta$ catenin and P53) as a new therapeutic approach [52]. Additionally, other types of alterations can occur that lead to an over-activation of the Wnt/ $\beta$ catenin pathway, one of the most frequent being a loss-of-function mutation in ZNRF3, a tumor-suppressor gene with a negative regulatory role in the Wnt/ $\beta$ catenin pathway. Blocking this signalling pathway has been shown to increase apoptosis as well as block steroidogenesis in ACC cells expressing the pS54P mutation *in vitro* [53]. Mice lacking ZNRF3 develop adrenocortical carcinomas, with the pro-tumoral effect of ZNRF3 inactivation occurring through the action of the protein Porcupine, which plays a key role in the secretion of Wnt ligands [54]. Porcupine inhibitors are in the process of being developed, with the aim of treating ACC carrying a ZNRF3 mutation. Recently, a study exploring the repurposing of drugs (an emerging concept where new indications are found for old drugs), identified a molecule with an anti-cancer effect that act through inhibition of the Wnt/ $\beta$ catenin signalling pathway. Rottlerin, a natural polyphenol isolated from the Asian tree *Mallotus philippensis*, inhibits proliferation and induces apoptosis in cell lines derived from ACC as well as in mouse xenograft models [55].

### 4.2. Inhibitors of the cyclin-dependent kinase (CDK) signalling pathway

The cell cycle is regulated by several key proteins, notably by cyclin-dependent kinases (CDK), which are targets for cell cycle checkpoint inhibitors that have recently been discovered.

Several studies have reported that alterations in the oncogene CDK4 may be frequent in ACC, with a prevalence of between 7% and 40% [9,28,49,50,56]. Over-expression of CDK4 has also been shown at the protein level in ACC [57]. These observations suggest a potential role for CDK4/6 inhibitors, such as palbociclib, ribociclib and abemaciclib, as promising candidates for management of ACC. Additionally, palbociclib has been shown to have an effect on cell viability in cell lines derived from ACC (NCI-H295R, SW13 and MUC1) as well as in primary cultures [57–59]. Palbociclib is currently approved by the FDA for use in treatment of locally advanced and metastatic breast cancers, with an acceptable level of toxicity. It would be of interest to investigate this drug as a potential novel therapeutic option for the treatment of ACC.

### 4.3. Inhibitors of the Notch signalling pathway

Genomic alterations in genes of the signalling pathway for Notch (gain of copy number for JAG1 and NOTCH1) are frequently identified in ACC [10,60]. Additionally, over-expression of proteins of the Notch pathway, JAG1, activated NOTCH1 and HEY2, have also been reported in ACC compared to normal adrenal tissue or adrenocortical adenoma [61]. This suggests a role for this signalling pathway in tumorigenesis. Clinical trials have tested several gamma-secretase inhibitors (GSI), which inhibit the Notch pathway by blocking cleavage of the transmembrane domain of Notch, in various solid tumors though not specifically in ACC [62]. Future studies are thus needed to explore the role of GSI in patients with ACC.

### 4.4. Inhibitors of MAP/ERK signalling pathway

#### 4.4.1. NF1

Neurofibromin 1 (NF1) is a protein that plays a role in an inhibitory pathway of the proto-oncogene RAS. In fact, an alteration in NF1 leads to over-activation of the Ras/Raf/MEK/ERK pathway that has been implicated in tumorigenesis. Neurofibromatosis type 1 (NF1) is a neuro-cutaneous syndrome that predisposes subjects to several benign and/or malignant tumors. Adrenocortical carcinoma has been reported only rarely in patients presenting with NF1. In sporadic ACC, mutations in NF1 that lead to a loss of function have been observed in around 10% of cases [9,10,49]. This data is of interest since NF1 could represent a therapeutic target for MAPK/ERK signalling pathway inhibitors (MEKi). Additionally, it has been shown that inhibition of MEK1 by PD184352 significantly reduces cell proliferation as well as steroidogenesis in the H295R ACC cell line [63]. Further studies are now required to evaluate the potential role of MEKi in ACC.

#### 4.4.2. BRAF

The serine/threonine kinase B-Raf plays a key role in the Ras/Raf/MEK/ERK signalling pathway. Activating mutations of the proto-oncogene BRAF have been found in numerous cancers. It has been shown, using DNA sequencing data, that activating mutations of BRAF are present in 2% to 6% of the ACC cases that have been studied [9,49,64]. This observation is of interest since the V600E BRAF mutation represents a therapeutic target for BRAF inhibitors. In fact, vemurafenib, lenvorenafenib and dabrafenib have been approved by the FDA for the treatment of metastatic melanomas that carry the V600E BRAF mutation. Therefore, specific inhibitors of the Ras/Raf/MEK/ERK pathway could be candidates for future clinical

trials in patients with ACC who are carefully selected based on their BRAF mutation status.

#### 4.5. PARP inhibitors

Genes that play a role in DNA repair (DNA damage repair genes, DDR) play a key role in maintaining genomic stability. Conversely, alterations in DNA repair mechanisms are involved in tumorigenesis, tumor progression and the response to therapy. Drugs that inhibit the protein, poly ADP-ribose polymerase (PARP1) can cause multiple breaks in double-stranded DNA and, in tumors expressing BRCA1, BRCA2 or PALB2 mutations, these double-strand breaks, which cannot be repaired, result in cellular apoptosis. PARP inhibitors are approved by the FDA for treatment of solid tumors with germline mutations in BRCA (olaparib and rucaparib for ovarian carcinomas, talazoparib for breast cancer). Additionally, a deficit in ATM, a protein kinase that plays a key role in DNA repair mechanisms secondary to double-strand breaks, has been reported to be associated with increased efficacy of olaparib in a number of cancers [65]. In ACC, somatic mutations in BRCA1, BRCA2 and ATM have been reported in around 4% of cases [50]. However, there have been no reported preclinical studies, to date, evaluating the efficacy of PARPi in ACC.

#### 4.6. Yttrium-90/lutetium-177-DOTATOC ( $^{90}\text{Y}/^{177}\text{Lu}$ -DOTATOC)

A very recent study has evaluated the potential benefit of  $^{90}\text{Y}$ - $^{177}\text{Lu}$ -DOTATOC as peptide receptor radionuclide therapy (PRRT) in 19 patients with advanced ACC. Initially, only the patients presenting with strong tumoral uptake of  $^{68}\text{Ga}$ -DOTATOC, indicating an over-expression of somatostatin receptors, showed a treatment benefit. Two patients (11%) were therefore treated with PRRT and showed stable disease for 4 and 12 months, respectively [66]. PRRT, through its interaction with somatostatinergic receptors, could thus represent a treatment option in patients with ACC who are pre-selected based on specific imaging characteristics.

### 5. Conclusion

A great deal of research has been carried out with the aim of finding new therapies for the management of advanced ACC. However, to date, results of these studies have been disappointing, and treatment with mitotane, with or without addition of E(D)P chemotherapy, remains the standard therapy. To explain this lack of success, it is well-established that ACC is a highly heterogeneous disease, and for this reason therapeutic approaches targeting single disease mechanisms may have failed. In order to remedy this, our understanding of the heterogeneity of the disease, at a molecular level, needs to be rapidly improved. Therapeutic approaches that use drugs in combination need to be evaluated in the hope of stopping these aggressive tumors by simultaneously targeting multiple pathways. Another possible explanation for the failure of novel therapies is that several of them (including all of the TKI drugs) are metabolised by CYP3A4 and that even minimal concentrations of mitotane are sufficient to reduce the efficacy of these therapies [67,68]. Lastly, it is important that viable predictive biomarkers are identified which will facilitate truly personalised treatments for this rare disease. Such research projects will succeed only when they are carried out as part of a multicentric effort, as part of ENDOCAN-COMETE and ENS@T.

#### Disclosure of interest

The authors declare that they have no competing interest.

### Acknowledgements

This paper was produced with institutional support provided by Ipsen Pharma, the first author having been a participant in Must de l'Endocrinologie 2020.

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