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REVIEW

5th International ACC Symposium: Future and Current Therapeutic Trials in Adrenocortical Carcinoma

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Abstract Adrenocortical carcinoma (ACC) is a rare and complex disease associated with a high mortality rate. Despite intensive translational and clinical research, prognosis remains poor. Over the past decade, a significant effort has been made to develop multinational, collaborative studies to better understand the pathogenesis and clinical features of this rare disease in attempt to improve the therapeutic strategies and patient outcome. The results of both standard and newer treatments are discussed in this review as well as the recent discovery of pathways involved in ACC pathogenesis that provide the rationale to introduce new molecular target therapies. Finally, remaining issues regarding how to improve available therapies in adjuvant setting are raised and addressed.

Introduction

Adrenocortical carcinoma (ACC) is a rare and complex disease associated with a high mortality rate. Despite intensive translational and clinical research, prognosis remains poor. Retrospective studies reveal a 5-year survival rate of approximately 65 % for patients stages I and II and 24 and 0 % for patients stages III and IV, respectively [1, 2]. While surgery is the only potential curative treatment for stage I and II disease, a significant amount of patients will recur and eventually die from disease. Over the past decade, a significant effort has been made to develop multinational, collaborative studies to better understand the pathogenesis and clinical features of this rare disease in attempt to improve outcome.

The goal of this review is to discuss current and potentially new treatments for advanced adrenocortical cancer discussed at the 5th International Adrenal Cancer Symposium at Ann Arbor in October 2015.

5th International ACC Symposium Session: something old, something new, something borrowed, what is true?

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Standard Treatment of Adrenocortical Cancer

Local Disease

Complete surgical resection of primary tumor is the only curative treatment. However, recurrence rate is high in patients that undergo primary resection, 30–50 % in patients with complete resection (R0) and up to 80 % in patients with incomplete resection (microscopic disease at surgical margins—R1) [1, 2]. Because of this high risk of recurrence, adjuvant treatment is of utmost importance. Mitotane remains the main adjuvant treatment. The best study that investigated the role of mitotane in the adjuvant setting was a retrospective analysis of 177 patients that had undergone surgical resection in Italy and Germany [3]. Recurrence-free survival was compared between 47 Italian patients treated with mitotane to 130 patients not treated with mitotane. Baseline features were similar between mitotane and control groups except for age and tumor staging in German patients; they were significantly older and had more stage I and II disease. Median recurrence-free

survival was significantly longer in mitotane group, 42 months as compared with 10 months in Italian control group and 25 months in German control group [3]. Based on these results, the use of mitotane in the adjuvant setting has been employed worldwide and is currently recommended for patients with potential residual disease (R1 or RX resection) and in patients with R0 resection but with high-risk disease, defined by a ki-67 index greater than 10 % [4]. The question whether mitotane is also useful in patients with R0 resection and Ki-67 index lower than 10 % remains unknown and is under investigation in the ADIUVO trial (www.adiuvo-trial.org; NCT00777244) which status was updated at this meeting. This is a prospective randomized study which is currently recruiting at different European and North American centers; the primary objective is to compare the results of adjuvant mitotane versus no treatment on recurrence-free survival in patients with low and intermediate risk of recurrence, defined by stage I-III ACC, R0, and ki-67 <10 %.

Another potential adjuvant treatment, discussed at this meeting, is postoperative radiotherapy to the adrenal bed. Over the past 10 years, 4 retrospective studies have investigated the role of radiation therapy in local control of disease. In the study by Fassnacht et al, 14 patients were treated with adjuvant postoperative radiotherapy and local control was reported in 12/14 (86 %) [5]. In 2011, Salboch et al reported the rate of local failure in 48 patients with resectable ACC treated at the University of Michigan Adrenal Cancer Clinic; 16 of 38 patients treated with surgery alone (33.3 %) and 2 of 10 (20 %) patients treated with surgery and adjuvant radiotherapy developed local failure suggesting a potential role of radiotherapy in reducing the risk of local recurrence [6]. In a subsequent retrospective study, this group has again demonstrated a potential role of radiotherapy in controlling local disease. In this study, two groups of patients ($N=20$ each group) were matched for stage at diagnosis, tumor grade, surgical margins status, and adjuvant use of mitotane. Local recurrence was observed in 1/20 (5 %) patients treated with radiation therapy and in 12/20 (60 %) patients not treated with radiation therapy ($P=.0005$; hazard ratio [HR] 12.59; 95 % confidence interval [CI] 1.62–97.88) [7]. Despite this excellent outcome, the authors could not demonstrate improvement of recurrence-free survival and overall survival between groups indicating that the ideal adjuvant therapy will be one that not only would prevent local recurrence but would also provide systemic control of disease. Except for the MD Anderson experience on postoperative radiotherapy [8], all reported retrospective series indicate a potential benefit of radiation therapy in reducing local recurrence; what further studies will need to address is whether there is a group of patients that local control is sufficient to result in gain of overall survival.

Advanced Disease

Patients with advanced disease defined as locally advanced disease (stage III) and metastatic disease (stage IV) represent up to 45 % of patients at diagnosis. In addition, a significant percentage of patients, with stage I and II disease at diagnosis, will eventually recur and require treatment [4]. Prognosis of these patients is dismal and 5-year survival rate is less than 15 % [4]. Despite advances in clinical research, treatment for metastatic ACC remains limited as no treatment regimen has resulted in better overall survival; in addition, all regimens are associated with adverse events that potentially impair quality of life.

In patients with small volume and indolent disease, local treatment modalities including surgery, radiotherapy, and interventional therapies should be considered whenever possible in addition to mitotane as systemic treatment. Mitotane is the only FDA-approved drug; as monotherapy, the response rate based on retrospective series averages 32 % [9, 10]; however, both progression-free survival and overall survival with mitotane alone are unknown.

In patients who failed mitotane as adjuvant therapy or patients with large tumor burden and rapidly progressive disease, treatment with systemic chemotherapy should be considered [4]. The FIRM-ACT trial is the first phase III prospective study that investigated the efficacy of two different regimens based on results from phase II studies: cisplatin, etoposide plus mitotane (EDP-M) versus streptozotocin plus mitotane (Sz + M) [11]. Progression-free survival was longer in patients treated with EDP-M compared to patients treated with Sz + M (5.0 vs 2.1 months). Based on these results, EDP-M became the first line regimen recommended for patients with progressive metastatic disease. Upon progression with this regimen, an option includes gemcitabine with capecitabine [12] and if available, inclusion in a clinical trial should be considered.

The Search for New Therapies

Molecular Target and Results of Molecular Target Therapies in ACC

Despite insufficient knowledge about the biology of this disease, the lack of an effective therapy was a driver for searching potentially new drugs. Several phase II studies were performed to investigate the role of molecular target therapies in advanced ACC [12–18]. Unfortunately, inhibition of epidermal growth factor receptor (EGFR), mammalian target of rapamycin (mTOR), insulin-like growth factor 1 receptor (IGF-1R), fibroblast growth factor receptor, and vascular endothelial growth factor (VEGF) pathways as a whole was not associated with clinical benefit (Table 1).

One particular target therapy important to be discussed is the inhibition of the IGF system. It is well documented the importance of the insulin-like growth factor system in ACC tumorigenesis. Both insulin growth factor 2 (IGF2) and its receptor insulin-like growth factor receptor 1 (IGF1R) are highly expressed in ACC, and preclinical studies did demonstrate that inhibition of this receptor resulted in reduced cell proliferation and increased apoptosis [21–23]. Based on these data and phase I data, a randomized placebo-controlled phase 3 study was performed to investigate the efficacy of linsitinib, an oral tyrosine kinase inhibitor of both IGF-1R and insulin receptor in 139 patients with locally advanced or metastatic ACC [20]. Despite being based on a firm rational, no difference was observed in progression-free survival or overall survival between patients treated with linsitinib ($N=90$) versus placebo ($n=49$). Similar results were obtained in a phase II trial that investigated cixutumumab, a recombinant human IgG1 monoclonal antibody directed at the IGF1R, in combination with mitotane in 20 patients with advanced ACC [19]. Further studies are necessary to understand molecular mechanisms of resistance to IGF1R inhibitors and to identify the subgroup of patients that will potentially benefit from this therapeutic intervention.

The combination of cixutumumab and temsirolimus was investigated in an extended phase I study including 26 patients with metastatic adrenal cancer; more than 40 % of patients had durable stable disease and time to progression was 9 months [24] (Table 1). These results seem promising, and this combination deserves to be further developed.

Inhibition of cholesterol esterification is another treatment modality being investigated in patients with adrenal cancer and discussed at this meeting. ATR-101 is a selective and potent inhibitor of acyl-coenzyme A:cholesterol O-acyltransferase 1 (ACAT1), an enzyme that catalyzes esterification of intracellular free cholesterol. The inhibition of cholesterol esterification and the buildup of free intracellular cholesterol is one of the mechanisms by which this drug results in activation of the apoptotic pathway and cell death [25]. In addition, preclinical studies indicate that it results in decreased steroid production. A phase I/II study is ongoing to investigate the tolerability and initial efficacy of this drug in ACC patients (NCT01898715) (Table 2).

Over the past 10 years, through intensive basic research, much progress has been made in defining molecular abnormalities important for the development of adrenal cortical cancer. The major breakthrough in trying to better understand ACC pathogenesis and its heterogeneous outcome comes from the recently published Cancer Genome Atlas (TCGA) Research Network that evaluated genomic profile of ACCs correlating with clinicopathological features [26]. In agreement with the observed clinical and prognostic heterogeneity of ACC, it has been observed that the genomic landscape is also complex but certain genetic alterations can define subgroups of tumors with different clinical characteristics and outcomes. Alterations in driver genes such as ZNRF3, TP53, and CTNNB1 are associated with poor outcome as well as the presence of hypermethylation in gene promoter regions. These molecular abnormalities result in differential activation of distinct pathways including WNT/β-catenin signaling pathway, the IGF system, and the G1/S checkpoint pathway. Based on this knowledge, research should focus on identification of drugs that will target these pathways, and clinical trials should attempt to individualize treatment according to specific genomic signature profiles.

New Molecular Targets and New Therapies

Several issues can be taken into account to explain why molecular target therapies up to now substantially failed to be efficacious in the management of ACC patients, despite the strong rationale. The trials have included heavily pretreated cases that are notoriously poorly responsive to any kind of therapy. The majority of patients have been treated with mitotane which biological activity can persist for months after the drug withdrawal. This was an important limitation particularly for studies that tested small molecular target agents that

Table 1 Clinical studies investigating target therapies in ACC

Target therapy (reference)	Target	Study phase	Number of patients	Response	Median survival
Sunitinib [16]	VEGFR, RET, RET/PTC	II	38	SD 5/38 PD 24/38 6 deaths prior to evaluation	PFS 2.8 months
Axitinib [17]	VEGFR	II	13	SD 8/13 (>3 months)	PFS 5.8 months
Sorafenib + paclitaxel [13]	VEGFR, RET, BRAF	II	10	PD 90 %	NR
Cixutumumab + temsirolimus [19]	IGF1R + mTOR	I	26	SD 42 % (>6 months)	TTP 9 months
Cixutumumab + mitotane [20]	IGF1R	II	20	PR 5 % SD 35 %	PFS 1.5 months
Linsitinib [21]	IGF-1R	III	139 (90 linsitinib/ 49 placebo)	PR 3 % SD 6.7 % (>6 months)	PFS 44 days linsitinib vs 46 days placebo

Abbreviations: *PR* partial response, *SD* stable disease, *PD* progressive disease, *PFS* progression-free survival, *TTP* time to progression

Table 2 Ongoing and proposed new trials in ACC

Drug	Target	Study phase	Tumor type	Mechanism of action
Avelumab (NCT01772004)	PD-L1	I	Solid tumors including ACC	Immunotherapy
Ipilimumab + radiotherapy (NCT02239900)	CTLA-4	I/II	Solid tumors including ACC	Immunotherapy
Pembrolizumab* (pre-accrual)	PD-L1	II	ACC	Immunotherapy
ATR-101 (NCT01898715)	ACAT-1	I/II	ACC	Inhibition of cholesterol esterification
BBI608 + paclitaxel (NCT01325441)	Cancer stem cell inhibitor	I/II	Solid tumors including ACC	Inhibition of Stat 3, β catenin and Nanog pathways

*Proposed trials at Memorial Sloan Kettering and at University of Texas MD Anderson Cancer Center

are substrates of the p450-dependent enzyme CYP3A4, notoriously induced by mitotane. Of course, we could not exclude that the molecular target compounds tested up to now may be simply not efficacious in the treatment of ACC [27]. New molecules and new targets are therefore needed [28]. The study by Assiè and colleagues has confirmed the role of *CTNNB1*, *TP53*, *CDKN2A*, *RB1*, and *MEN1* in the pathogenesis of ACC and has detected new genes such as *ZNRF3*, *DAXX*, *TERT*, and *MED12* [26]. *These genes* activate several key pathways. The most frequent are WNT/β-catenin (*ZNRF3* and *CTNNB1*) (39 %) *followed by p53* (16 %) *CDKN2A* (11 %), and *RB1* (7 %).

WNT signaling regulates diverse developmental and homeostatic functions, including proliferation, differentiation, cell polarity, motility, and migration. It is therefore an attractive therapeutic target for many malignancies. Research initially focused on downstream WNT/β-catenin pathway inhibitors such as tankyrase inhibitors and many others. This group of drugs however demonstrated severe toxicities, particularly GI toxicity. Upstream inhibitors of WNT production and function are more promising and less toxic. They comprise monoclonal antibodies and decoy receptors that can block the interaction of WNTs with its receptors or alternatively small molecules that prevent WNT ligand biogenesis and secretion. Among the latter, the most important are inhibitors of PORCN, an enzyme that adds a mono-unsaturated palmitoleate moiety to a serine residue conserved in all mammalian WNTs. This palmitoleation is essential for both WNT secretion and the binding of WNTs to their receptors. Overall, drugs targeting the WNT/β-catenin pathway are currently in early development and still not available for the clinical use in ACC patients [29].

Drugs targeting the cell cycle such as the cyclin-dependent kinase inhibitors could be another new therapeutic approach [30, 31]. Among them palbociclib is an oral, highly selective inhibitor of CDK 4/6 that is in advanced development. In patients with metastatic estrogen receptor-positive, HER2-negative breast cancer, the drug administered in combination with letrozole (Phase II; PALOMA-1) or with fulvestrant (Phase III; PALOMA-3) has significantly prolonged progression-free survival in comparison to letrozole, or fulvestrant alone, respectively [30]. This drug and other drugs of the same class are currently being tested in several malignancies [31].

Moreover, PI3K/mTOR pathway that is downstream to IGFR is important in the proliferation activity and survival of ACC. Drugs targeting this pathway either alone or in association with IGFR inhibitors deserve to be tested in ACC. The preliminary data on the activity of the association of cixutumumab, a monoclonal antibody targeting IGFR, with temsirolimus, as previously mentioned, are promising [24].

Italian researchers have identified the transcription factor estrogen-related receptor alpha (ERRα) as an additional potential target due to its ability to regulate energy metabolism, mitochondrial biogenesis, and signaling related to cancer progression. Therapeutic strategies targeting ERRα could represent an innovative/alternative therapy for the treatment of ACC [32].

A recent study showed for the first time an increased HGF/cMET expression in human adrenocortical carcinoma samples and activation of HGF/cMET enhanced ACC growth, tumor-related angiogenesis, and cell survival. cMET therefore may be a valuable therapeutic target for this disease [33]. In this paper in fact, the pharmacologic inhibition of cMET suppressed cell proliferation and tumor growth. Several monoclonal antibodies and small molecule tyrosine kinase inhibitors targeting cMET are in the latter stages of clinical development for gastrointestinal cancer, lung cancer, and hepatocellular carcinoma, and other drugs are currently on development. Noteworthy, this paper demonstrated that exposure of ACC cells to currently available therapeutic strategies in clinics such as mitotane, cisplatin, or radiation, rapidly induced cMET expression. The dynamic increase of cMET expression as a consequence of tumor exposure to antineoplastic therapy is not new. In prostate cancer patients, long-term androgen deprivation results in the upregulation of cMET and this switch of signaling pathway is associated with a more aggressive disease state and increased metastatic behavior [34].

cMET therefore represents a molecular pathway that is implicated in the anticancer drug response and resistance. In ACC, cMET inhibitors appear to be appealing in future clinical trials of patients with disease progression to standard antineoplastic therapies, i.e., EDP-M and mitotane. Along this line, it is noteworthy to mention that in patients with renal cell carcinoma, the prospective randomized phase III trial METEOR showed that a cMET inhibitor cabozantinib significantly improved progression-free survival and overall survival over the standard therapy everolimus as second line approach after progression to first line antiangiogenetic therapies [35].

The rapid advance in molecular understanding of host-tumor interaction has defined a new range of targets for antibody development. The striking improvement of knowledge in immunology has led to the identification of immunomodulatory antibodies that directly enhance the function of T cells. These agents are commonly called "checkpoint inhibitors" because they block normally negative regulators of T cell immunity such as cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed death receptor-1 (PD-1). Although both strategies work by restarting an effective antitumor immune response, PD-1 inhibitors have obtained better antitumor efficacy than CTLA-4 inhibitors [36]. The interaction between PD-1, expressed on lymphocytes and dendritic cells and PD-L1 ligand, expressed by tumor cells results in a downregulation of the T cell response. Therefore, the PD-1/PD-L1 axis inhibition by targeted antibodies represents a very promising mechanism to stimulate the antitumor activity of the immune system, improving the outcomes of cancer patients. The checkpoint blocking antibodies against PD-1 have demonstrated significant efficacy in the treatment of an expanding list of malignancies, and the most relevant results have been obtained in the management of patients with advanced melanoma, non-small cell lung cancer (both squamous and adenocarcinoma), and kidney cancer [37]. Drugs targeting PDL-1 are currently being tested in phase II-III clinical trials. Table 2 lists trials that patients with ACC could be enrolled. Unfortunately, not all patients respond to these therapies, and the future use of immune checkpoint inhibitors in cancer patients has to be molecularly supported.

A recent study assessed PD-L1 positivity by immunohistochemistry in 28 patients with surgically treated ACC. Expression was observed in approximately 11 % of ACC cases and did not correlate with stage at diagnosis (UICC or ENSAT), grade, and hormone secretion. In addition, no correlations were found between PD-L1 expression and survival at 5 years [38]. On the bases of these very preliminary results, ACC seems to be not a candidate for these drugs; however, we are only at the beginning, and it is well known that PD-L1 expression in tumor cells can be upregulated by pretreatment with cytotoxic agents and other immunologic therapies such as interferon gamma.

Future Perspectives

As discussed, ACC is a very aggressive disease that is difficult to treat. Surgery is the only therapy that offers cure. However, the majority of ACC patients radically resected are destined to recur, most of them within the first 2 years. The development of adjuvant strategies has the greatest possibility to modify the natural history of the disease. As previously mentioned, the most relevant data to support the efficacy of adjuvant mitotane is a case control study that compared the outcome of patients followed in centers that systematically prescribed mitotane to all radically resected patients with that of patients followed in centers that did not [3]. Despite the limitation of this study, adjuvant mitotane is currently recommended by international guidelines for patients with moderate/high risk of disease relapse [4]. Mitotane efficacy, however, is slowly acquired since several weeks are needed until attaining adequate therapeutic concentration. This implies that a rapidly proliferating ACC radically operated and submitted to adjuvant mitotane can potentially recur before serum mitotane level attains the so-called therapeutic concentration. The combination of mitotane and chemotherapy can allow a rapid antiproliferative activity with chemotherapy and long-term therapeutic efficacy with mitotane maintenance. A randomized trial testing mitotane versus the combination of mitotane and chemotherapy is therefore an unmet need.

Another important issue is that we are currently selecting patients to be addressed to adjuvant mitotane on the basis of the risk of relapse and/or death. However, only a minority of radically operated patients are considered at low risk and therefore not addressed to mitotane. Adjuvant mitotane therapy is usually prescribed for at least 2 years and the drug is toxic and may reduce patient's quality of life. In addition, it needs frequent drug monitoring and a complex regimen of steroid replacement and management of adverse events. There is an urgent need for a predictive factor in order to select patients to be addressed to adjuvant mitotane among those whose disease is destined to obtain a benefit from the therapy. Despite mitotane is currently adopted in the management of ACC for many decades, the mechanism of antineoplastic activity is still not clear and this limits the identification of molecular predictive factors. Two papers recently published have identified predictive factors of adjuvant mitotane efficacy. One of them provided in vitro and in vivo evidence of a relationship between Ribonucleotide Reductase Large Subunit 1 (RRM1) enzyme and the antineoplastic activity of mitotane in ACC [39]. RRM1 enzyme is involved in the synthesis of deoxyribonucleotides for DNA synthesis and represents the cellular target for gemcitabine. The second paper identified CYP2W1 enzyme that is highly expressed in both normal and neoplastic adrenal glands as a new predictive marker for the response to mitotane treatment [40]. Both these predictive markers need to be validated in prospective randomized adjuvant studies.

In conclusion, a future strategy in the management of ACC should be the assessment of efficacy in adjuvant setting of standard therapies currently adopted in advanced disease. There are several examples in medical oncology of drugs that are not particularly efficacious in advanced disease in which their efficacy is enhanced in adjuvant setting. Advanced ACC patients should be preferably addressed to prospective clinical trials testing new molecular target agents.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests.

References

1. Fassnacht M, Johanssen S, Quinkler M (2009) German adrenocortical carcinoma registry group, European Network for the study of adrenal tumors. Limited prognostic value of the 2004 International Union Against Cancer staging classification for adrenocortical carcinoma: proposal for a revised TNM classification. Cancer 115:243–250
2. Libé R, Borget I, Ronchi CL et al (2015) Prognostic factors in stage III–IV adrenocortical carcinomas (ACC): an European Network for the Study of Adrenal Tumor (ENSAT) study. Ann Oncol 26:2119–2125
3. Terzolo M, Angeli A, Fassnacht M et al (2007) Adjuvant mitotane treatment for adrenocortical carcinoma. N Engl J Med 356:2372–2380
4. Berruti A, Baudin E, Gelderblom H (2012) Adrenal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 23(7):vii131–vii138
5. Fassnacht M, Hahner S, Polat B et al (2006) Efficacy of adjuvant radiotherapy of the tumor bed on local recurrence of adrenocortical carcinoma. J Clin Endocrinol Metab 91:4501–4504
6. Sabolch A, Feng M, Griffith K et al (2011) Adjuvant and definitive radiotherapy for adrenocortical carcinoma. Int J Radiat Oncol Biol Phys 80:1477–1484
7. Sabolch A, Else T, Griffith KA et al (2015) Adjuvant radiation therapy improves local control after surgical resection in patients with localized adrenocortical carcinoma. Int J Radiat Oncol Biol Phys 92(2):252–259
8. Habra MA, Ejaz S, Feng L et al (2013) A retrospective cohort analysis of the efficacy of adjuvant radiotherapy after primary surgical resection in patients with adrenocortical carcinoma. J Clin Endocrinol Metab 98:192–197
9. Baudin E, Leboulleux S, Al Ghuzlan A et al (2011) Therapeutic management of advanced adrenocortical carcinoma: what do we know in 2011? Horm Cancer 6:363–371
10. Kerkhofs TMA, Ettaieb MHT, Hermsen IGC, Haak HR (2015) Developing treatment for adrenocortical carcinoma. Endocrine-Relat Cancer 22:325–338
11. Fassnacht M, Terzolo M, Allolio B et al (2012) Combination chemotherapy in advanced adrenocortical carcinoma. N Engl J Med 366:2189–2197
12. Sperone P, Ferrero A, Daffara F et al (2010) Gemcitabine plus metronomic 5-fluorouracil or capecitabine as a second-/third-line chemotherapy in advanced adrenocortical carcinoma: a multicenter phase II study. Endocrine-Relat Cancer 17:445–453
13. Berruti A, Sperone P, Ferrero A, Germano A, Ardito A, Priola AM, De Francia S, Volante M, Daffara F, Generali D et al (2012) Phase II study of weekly paclitaxel and sorafenib as second/third line therapy in patients with adrenocortical carcinoma. Eur J Endocrinol 166:451–458
14. Wortmann S, Quinkler M, Ritter C et al (2012) Bevacizumab plus capecitabine as a salvage therapy in advanced adrenocortical carcinoma. Eur J Endocrinol 162:349–356
15. Gross DJ, Munter G, Bitan M et al (2006) The role of imatinib mesylate (Glivec) for treatment of patients with malignant endocrine tumors positive for c-kit or PDGF-R. Endocrine-Relat Cancer 13:535–540
16. Kroiss M, Quinkler M, Johanssen S et al (2012) Sunitinib in refractory adrenocortical carcinoma: a phase II, single-arm, open-label trial. J Clin Endocrinol Metab 97:3495–3503
17. O'Sullivan C, Edgerly M, Velarde M et al (2014) The VEGF inhibitor axitinib has limited effectiveness as a therapy for adrenocortical cancer. J Clin Endocrinol Metab 99(4):1291–1297
18. Quinkler M, Hahner S, Wortmann S et al (2008) Treatment of advanced adrenocortical carcinoma with erlotinib plus gemcitabine. J Clin Endocrinol Metabol 93:2057–2062
19. Lerario AM, Worden FP, Ramm CA et al (2014) The combination of insulin-like growth factor receptor 1 (IGF1R) antibody cixutumumab and mitotane as a first-line therapy for patients with recurrent/metastatic adrenocortical carcinoma: a multiinstitutional NCI-sponsored trial. Horm Cancer 5:232–239
20. Fassnacht M, Berruti A, Baudin E et al (2015) Linsitinib (OSI-906) versus placebo for patients with locally advanced or metastatic adrenocortical carcinoma: a double-blind, randomised, phase 3 study. Lancet Oncol 16:426–435
21. Haluska P, Worden F, Olmos D et al (2010) Safety, tolerability, and pharmacokinetics of the anti-IGF-1R monoclonal antibody figitumumab in patients with refractory adrenocortical carcinoma. Cancer Chemother Pharmacol 65:765–773
22. de Fraipont F, El Atifi M, Cherradi N et al (2005) Gene expression profiling of human adrenocortical tumors using complementary deoxyribonucleic acid microarrays identifies several candidate genes as markers of malignancy. J Clin Endocrinol Metab 90:1819–1829
23. Barlaskar FM, Spalding AC, Heaton JH et al (2009) Preclinical targeting of the type I insulin-like growth factor receptor in adrenocortical carcinoma. J Clin Endocrinol Metab 94:204–212
24. Naing A, Lorusso P, Fu S et al (2013) Insulin growth factor receptor (IGF-1R) antibody cixutumumab combined with the mTOR inhibitor temsirolimus in patients with metastatic adrenocortical carcinoma. Br J Cancer 108(4):826–830
25. Floettmann JE, Buckett LK, Turnbull AV et al (2013) ACAT-selective and nonselective DGAT1 inhibition: adrenocortical effects—a cross-species comparison. Toxicol Pathol 41(7):941–950
26. Assie G, Letouze E, Fassnacht M et al (2014) Integrated genomic characterization of adrenocortical carcinoma. Nat Genet 46:607–612
27. Ferrari L, Grisanti S, Sigala S, Consoli F, Terzolo M, Berruti A (2014) Molecular target agents in adrenocortical carcinoma: rationale and difficulties in trial design. Int J Endo Oncol 1:31–34
28. De Martino MC, Al Ghuzlan A, Aubert S et al (2013) Molecular screening for a personalized treatment approach in advanced adrenocortical cancer. J Clin Endocrinol Metab 98:4080–4088
29. Madan B, Virshup DM (2015) Targeting Wnts at the source-new mechanisms, new biomarkers, new drugs. Mol Cancer Ther 14:1087–1094
30. Beaver JA, Amiri-Kordestani L, Charlab R et al (2015) FDA approval: palbociclib for the treatment of postmenopausal patients with estrogen receptor-positive, HER2-negative metastatic breast cancer. Clin Cancer Res 21:4760–4766
31. Tamura K (2015) Development of cell-cycle checkpoint therapy for solid tumors. Jpn J Clin Oncol
32. Casaburi I, Avena P, De Luca A et al (2015) Estrogen related receptor α (ERRα) a promising target for the therapy of adrenocortical carcinoma (ACC). Oncotarget 6(28):25135–25148

33. Phan LM, Fuentes-Mattei E (2015) Hepatocyte growth factor/cMET pathway activation enhances cancer hallmarks in adrenocortical carcinoma. Cancer Res 75(19):4131–4142
34. Pfeiffer MJ, Smit FP, Sedelaar JP, Schalken JA (2011) Steroidogenic enzymes and stem cell markers are upregulated during androgen deprivation in prostate cancer. Mol Med 17:657–664
35. Choueiri TK, Escudier B, Powles T, METEOR Investigators (2015) Cabozantinib versus everolimus in advanced renal-cell carcinoma. N Engl J Med 373(19):1814–1823
36. Buchbinder EI, Desai A (2015) CTLA-4 and PD-1 pathways: similarities, differences, and implications of their inhibition. Am J Clin Oncol
37. Li X, Hu W, Zheng X et al (2015) Emerging immune checkpoints for cancer therapy. Acta Oncol 10:1706–1713
38. Fay AP, Signoretti S, Callea M et al (2015) Programmed death ligand-1 expression in adrenocortical carcinoma: an exploratory biomarker study. J Immunother Cancer 3:3
39. Volante M, Terzolo M, Fassnacht M et al (2012) Ribonucleotide reductase large subunit (RRM1) gene expression may predict efficacy of adjuvant mitotane in adrenocortical cancer. Clin Cancer Res 18(12):3452–3461
40. Ronchi CL, Sbiera S, Volante M et al (2014) CYP2W1 is highly expressed in adrenal glands and is positively associated with the response to mitotane in adrenocortical carcinoma. PLoS One 9(8): e105855