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**Original Research**

# Chemo–immunotherapy with cisplatin and nivolumab as second-line approach in metastatic adrenocortical carcinoma

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## Abstract

***Context*** **No effective therapies are available for patients with advanced adrenocortical carcinoma (ACC) progressing after standard therapy: EDP (etoposide, adriamycin, and cisplatin) and mitotane (EDP-M regimen). These patients have poor prognosis with a median life expectancy of 6-7 months. Immunotherapy in this setting is promising. Concomitant chemotherapy administration can enhance the efficacy of immunotherapy, as demonstrated in other malignancies.**

***Objective*** **This retrospective study aims to explore the activity of a combination of cisplatin and nivolumab administered to patients with ACC who have previously undergone chemotherapy and mitotane treatment.**

***Patients and methods*** **Cisplatin, 25 mg/m$^2$ on day 1, and nivolumab, 240 mg on day 2, every 2 weeks, were administered to advanced/metastatic ACC with disease progression to EDP-M regimen plus/minus other chemotherapeutic regimens. The primary endpoint was the disease response according to RECIST. Secondary endpoints were clinical benefit, disease control rate (DCR), overall survival (OS), progression-free survival (PFS), and safety.**

***Results*** **Twenty-three patients were enrolled between January 2023 and March 2025. The median follow-up was 15.1 months. Eight patients [34.8% (95% CI, 15.3%-54.2%)] obtained a partial response and 4 patients (17.3%) a stable disease; therefore, 12 patients (52.2%) obtained a clinical benefit. The DCR after 6 months was obtained in 39.1% [95% CI, 19.7%-61.5%] of patients. The median PFS was 4.3 months [95% CI, 3.9-13.0], and the median OS was 18.9 months [95% CI, 15.8-not reached]. Chemo–immunotherapy combination was well tolerated, and most toxicities were limited to grade G1-2 according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) criteria. One patient discontinued treatment after 1 cycle, due to grade 3 immune-related hepatitis.**

***Conclusion*** **The combination of cisplatin and nivolumab is an active regimen in advanced, previously treated, ACC patients. The long survival achieved in this patient population with a poor prognosis is promising.**

**Keywords** adrenocortical carcinoma, immunotherapy, chemotherapy, combination treatments, immunoresistance, neuroendocrine tumor

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**Significance**

Adding chemotherapy to immunotherapy may be a viable strategy to overcome the intrinsic immunoresistance of adrenal cortical carcinoma (ACC), but it has never been explored in patients with this rare malignancy. In this single-center study in which 23 patients with previously pretreated metastatic ACC underwent the combination cisplatin + nivolumab, an objective response rate of 33% was achieved, and most importantly the median survival of the entire cohort was 19 months. Disease control has been achieved by 3 patients for 15 months or more. The results are promising and suggest that immunochemotherapy could be a potentially effective second-line treatment for patients with ACC.

# Introduction

Adrenocortical carcinoma (ACC) is an extremely rare disease with an estimated annual incidence of .5-2 new cases per million population per year.[1]

Surgery is the only therapeutic approach that offers patients a chance of cure, and it is the mainstay of therapy.

For patients with metastatic disease who are not eligible for surgery, systemic treatment consists of either mitotane alone[2] or mitotane in combination with etoposide, doxorubicin, and cisplatin (EDP-M) chemotherapy.[1,3]

Although some patients may achieve a complete pathological response with EDP-M chemotherapy, only a minority of them obtain long-term disease control.[4] According to the FIRM-ACT study, in fact, 25% of patients who underwent EDP-M experienced no progression after 12 months of treatment, and 15% of patients remained alive after 5 years.[5]

To date, there are no effective treatments for patients progressing after first-line therapy. Some studies have evaluated the efficacy of second-line chemotherapy regimens, such as the combination of gemcitabine and capecitabine,[6] temozolomide,[7] or cabazitaxel monotherapy,[8] but the results have been unsatisfactory.

Disappointing results have also been obtained with target therapies such as antiangiogenetic drugs: sunitinib[9] and axitinib[10] and insulin-like growth factor-1 inhibitors either alone[11,12] or in combination with mechanistic target of rapamycin inhibitors.[13] A recent small phase II study with cabozantinib resulted in potentially interesting results.[14] Nevertheless, confirmation is necessary for the observed progression-free survival (PFS) of 6 months and overall survival (OS) of 24 months.

The results of immunotherapy appear to be more promising. A recent meta-analysis of published studies, including 250 patients, showed that, although this treatment modality achieved an objective response rate (ORR) of only 14%, and a median PFS of just 2.8 months, the median OS was 14 months. This latter finding is encouraging, as it is approximately twice that reported for the great majority of the second-line therapies mentioned above.[15]

Advanced adrenocortical carcinoma is not considered an immunologically “hot tumor” due to several mechanisms.[16] In many types of cancer, chemotherapy has been combined with immunotherapy to overcome the immunosuppressive “cold” tumor microenvironment,[17] often with significant results, and this approach has become a therapeutic standard.[18,19]

The use of chemo–immunotherapy has yet to be tested in the treatment of patients with ACC.

This paper presents the findings of a retrospective analysis that evaluated the activity and efficacy of a combination of cisplatin and nivolumab in metastatic ACC with progressive disease (PD) to EDP-M.

# Patients and methods

## Study design and patient population

This monocentric observational retrospective study was conducted on consecutive patients with advanced ACC who underwent chemo–immunotherapy with cisplatin and nivolumab between January 2023 and March 2025 at the Medical Oncology Unit of the ASST-Spedali Civili, Università degli Studi di Brescia, Italy. Patients were given chemo–immunotherapy as their next treatment option after the standard treatment of EDP-M chemotherapy.

Patients were addressed to chemo–immunotherapy if they had histologically proven locally advanced or metastatic ACC not suitable for surgery (stage III-IV), age of 18 years or older, radiologically measurable disease according to RECIST 1.1 criteria, Eastern Cooperative Oncology Group (ECOG) performance status 0-2, adequate hematologic and biochemical function, and no history of other malignancies. (Detailed inclusion and exclusion criteria are provided in the Appendix).

The study was approved by the Ethical Review Board of ASST-Spedali Civili in Brescia (protocol number: NP6521) and was designed and conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. Written consent was obtained from each patient.

## Treatment administered

The chemo–immunotherapy regimen consisted of cisplatin, which was administered intravenously at a dose of 25 mg/m$^2$ on day 1 of each cycle, and nivolumab at a dose of 240 mg given intravenously at day 2. One cycle of the regimen was defined as a 2-week interval. Mitotane treatment was maintained associated with glucocorticoid replacement.

Nivolumab was purchased as an off-label drug from the ASST-Spedali Civili in Brescia.

Treatment was continued until disease progression, consent withdrawal, and unacceptable toxicity. Cisplatin was planned to be discontinued in case of grade 3-4 toxicities, worsening renal function particularly in patients with a single kidney, and upon reaching a cumulative dose of 600 mg, beyond which the risk of neurotoxicity significantly increases. In the absence of disease progression, nivolumab was continued for a maximum of 2 years.

**Table 1** Patients characteristics.

| Total patients, *n* | 23 |
|---|---|
| Sex, *n* (%) | |
| Male | 7 (30.4) |
| Female | 16 (69.6) |
| Age, years | 49 (32-69) |
| ECOG PS, *n* (%) | |
| 0 | 19 (82.6) |
| 1 | 4 (17.4) |
| Clinical presentation, *n* (%) | |
| Hormone symptoms | 6 (26.1) |
| Mass symptoms | 9 (39.1) |
| Incidentaloma | 8 (34.8) |
| Hormone secretion at diagnosis, *n* (%) | |
| No secretions | 14 (60.9) |
| Cortisol excess | 7 (30.4) |
| Androgens excess | 2 (8.7) |
| ENSAT stage at diagnosis, *n* (%) | |
| II | 9 (39.1) |
| III | 10 (43.5) |
| IV | 4 (17.4) |
| Previous surgery, *n* (%) | |
| No | 3 (13.0) |
| Yes | 20 (87.0) |
| Resection status, *n* (%) | |
| R0 | 15 (65.2) |
| R1 | 4 (17.4) |
| RX | 1 (4.3) |
| Adjuvant treatment, *n* (%) | |
| Mitotane | 18 (78.3) |
| EP plus mitotane | 2 (8.7) |
| No adjuvant treatment | 3 (13.0) |
| RFS, months | 8.7 (2-34.7) |
| First-line metastatic treatment, *n* (%) | |
| EDP-M | 22 (95.7) |
| Cisplatin only | 1 (4.3) |
| Best response to first-line therapy, *n* (%) | |
| PR | 6 (26.1) |
| SD | 12 (52.2) |
| PD | 5 (21.7) |
| Median number of first-line chemotherapy cycles | 5 (2-7) |
| Second-line metastatic treatment, *n* (%) | |
| Temozolomide | 4 (17.4) |
| Gemcitabine plus capecitabine | 1 (4.3) |
| Third-line metastatic treatment, *n* (%) | |
| Temozolomide | 1 (4.3) |
| Gemcitabine plus capecitabine | 2 (8.7) |
| *N* of chemotherapy lines, *n* | |
| 1 | 18 (78.3) |
| 2 | 2 (8.7) |
| 3 | 3 (13.0) |
| Time between end of EDP and start of CIS-NIVO | 7.5 (.9-57.4) |
| Mitotane in advanced setting, *n* (%) | 21 (91.3) |
| Mitotane levels at the start of CIS-NIVO, *n* (%) | |
| <14 mg/L | 13 (56.5) |
| >14 mg/L and <20 mg/L | 8 (34.8) |
| Median mitotane level at start of treatment (mg/L) | 12.8 (3.4-18.9) |
| Cortisol hypersecretion before CIS-NIVO, *n* (%) | 3 (13.0) |

Abbreviations: CIS-NIVO, cisplatin-nivolumab; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EDP-M, etoposide, doxorubicin, and cisplatin plus mitotane; ENSAT stage, European Network for the Study of Adrenal Tumours staging system; EP, etoposide-cisplatin; *n*, number; PD, progression disease; PR, partial response; RFS, relapse-free survival; SD, stable disease.

Premedication and antiemetic prophylaxis were recommended as per institutional guidelines.

Adverse events (AEs) were monitored throughout the study and reported using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03.

Physical examination, performance status, and routine laboratory tests were evaluated at baseline and during the combination treatment every 2 weeks, while mitotane plasma levels were evaluated at baseline and then every 2 months. All patients underwent an endocrine workup prior to starting therapy. Disease restaging by computed tomography (CT) scan was performed approximately every 12 weeks until disease progression or patient drop-out from the study. Disease response was assessed according to RECIST criteria (version 1.1).[20]

Patients who experienced progression but continued to benefit clinically as determined by the treating investigator stayed on therapy for another 8 weeks until radiological confirmation of progression. Once the study treatment was interrupted due to disease progression, the patients were followed for survival.

## Endpoints and statistical analysis

The primary endpoint of our study was the ORR according to RECIST 1.1 criteria. Secondary endpoints were clinical benefit rate (CBR), defined as the proportion of patients attaining a complete, partial, and stable disease (SD); disease control rate (DCR), defined as the proportion of patients attaining an objective response or disease stabilization as the best overall response lasting 6 months; PFS, defined as time from treatment initiation to progression by RECIST or death from any cause, or date of the last disease assessment in case of nonprogressing patients; OS, defined as time elapsing from treatment start to death for any causes or date of last follow-up; and drug combination safety according to NCI-CTCAE criteria.

Survival curves were calculated with the Kaplan–Meier estimator. Statistical analysis was performed with SPSS software (version 24.0, IBM Corp., Armonk, NY, USA).

# Results

## Patients characteristics

A total of 23 consecutive patients with advanced ACC, meeting the eligibility criteria, entered the study during the enrollment period. Their characteristics are summarized in Table 1.

The median follow-up for the cohort was 15.1 months [interquartile range (IQR), 7.3-20.1].

Women prevailed over males (69.6% vs 30.4%), and the median age was 49 years [range, 32-69].

Seven patients had cortisol-producing ACCs (30.4%) and 2 had androgen-producing ones (8.7%) at first diagnosis, and the remaining 14 (60.9%) patients had non–hormone-producing tumors. Prior to the initiation of chemo–immunotherapy, 3 patients (13.0%) presented with hypercortisolism and clinical features of Cushing's syndrome despite ongoing treatment with mitotane. They were additionally treated with metyrapone at doses ranging from 750 to 1500 mg/day.

Twenty patients (87.0%) had previously undergone adrenalectomy, with 14 (60.1%) performed via laparotomy and 6 (26.1%) via laparoscopy. Three patients (13.0%) were metastatic at first diagnosis. Eighteen patients (78.3%) received adjuvant mitotane after surgery, 2 patients (8.7%) received adjuvant therapy with etoposide-cisplatin (EP) plus mitotane as part of the ACACIA trial (NCT00058090), while 3 patients (13.0%) did not undergo any adjuvant treatment. The median relapse-free survival (mRFS) of the entire cohort was 8.7 months [range, 2.0-34.7].

All patients included had a radiologically PD before starting the cisplatin plus nivolumab regimen. Twenty-two patients (95.7%) had undergone first-line chemotherapy with the EDP-M regimen, while the remaining patients underwent cisplatin monotherapy due to contraindication to polychemotherapy. The median number of first-line chemotherapy cycles was 5 [range, 2-7]. Six patients (26.1%) had achieved a partial response (PR) to first-line chemotherapy, 12 (52.2%) had a SD, and 5 patients (21.7%) underwent disease progression. Overall, 18 patients (78.3%) received first-line chemotherapy before starting treatment with cisplatin and nivolumab. Two patients (8.7%) received second-line chemotherapy, and 3 patients (13.0%) received third-line chemotherapy with temozolomide in monotherapy or the combination gemcitabine plus capecitabine.

The median time between the end of first-line treatment with EDP and the initiation of chemo–immunotherapy combination was 7.5 months [range, .9-57.4].

## Treatment administered and toxicity

Table 2 shows the number of cycles of cisplatin and nivolumab administered and the reason for their suspension. The median number of cisplatin cycles was 8 [range, 4-22]. The reasons for discontinuation of this drug were disease progression in 14 patients (60.9%) and neurotoxicity in 6 patients (26.1%). The patients who stopped cisplatin therapy for reasons other than disease progression continued nivolumab administration for up to 2 years. Nivolumab was administered for a median number of 9 cycles [range, 4-39].

Chemo–immunotherapy combination was interrupted due to radiological disease progression in 16 patients (69.6%) and for completion of the 2 years in 1 patient. Six patients were still on treatment at the last follow-up date (Table 2).

The treatment was well tolerated. As depicted in Table 3, all patients had an AE of any grade; however, they were mild (G1 and G2) in most of them. The most common AEs were chemotherapy related, such as asthenia in 14 of patients (60.9%), nausea in 11 (47.8%), and paraesthesia in 7 (30.4%). While immunotherapy adverse effects occurred in a very small number of patients, they were mostly oral mucositis in 6 patients (26.1%) and rash in 2 (8.7%). Only 1 patient had G3 liver toxicity after 5 nivolumab administrations, leading to permanent treatment discontinuation also due to concomitant disease progression, and 2 patients (8.7%) presented an oral mucositis G3 requiring a temporary suspension.

**Table 2** Number of cycles of CIS-NIVO administered and the reason for their suspension.

| No. of cycles | Reason of withdrawal |
|---|---|
| 4 CIS-NIVO | Disease progression |
| 4 CIS-NIVO | Ongoing treatment |
| 5 CIS-NIVO | Disease progression |
| 5 CIS-NIVO | Disease progression |
| 5 CIS-NIVO | Disease progression |
| 5 CIS-NIVO | Disease progression and G3 hepatic toxicity |
| 5 CIS-NIVO +5 NIVO maintenance | Ongoing treatment. The patient is continuing platinum-free therapy due to neurotoxicity and renal toxicity |
| 6 CIS-NIVO | Disease progression |
| 6 CIS-NIVO +1 NIVO maintenance | Ongoing treatment. The patient is continuing platinum-free therapy due to mucositis |
| 7 CIS-NIVO | Disease progression |
| 7 CIS-NIVO | Disease progression |
| 8 CIS-NIVO | Disease progression. The patient underwent surgery |
| 8 CIS-NIVO | Ongoing treatment |
| 11 CIS-NIVO | Disease progression |
| 11 CIS-NIVO | Disease progression. The patient underwent surgery |
| 11 CIS-NIVO +10 NIVO maintenance | Ongoing treatment. The patient is continuing platinum-free therapy due to neurotoxicity |
| 11 CIS-NIVO +3 NIVO maintenance | Disease progression. Cisplatin had been discontinued due to neurotoxicity |
| 12 CIS-NIVO +1 NIVO maintenance | Disease oligoprogression. The patient underwent TACE on progressive liver lesions |
| 12 CIS-NIVO +4 NIVO maintenance | Disease progression. Cisplatin had been discontinued due to neurotoxicity |
| 14 CIS-NIVO +13 NIVO maintenance | Ongoing treatment. The patient is continuing platinum-free therapy due to neurotoxicity |
| 17 CIS-NIVO | Disease progression |
| 18 CIS-NIVO +4 NIVO maintenance | Disease oligoprogression. The PD lesion in psoas muscle was surgically removed |
| 22 CIS-NIVO +17 NIVO maintenance | Completion of 2 years of treatment |

Abbreviation: CIS-NIVO, cisplatin-nivolumab.

**Table 3** Adverse events related to CIS-NIVO.

| | All grades | G1 | G2 | G3 |
|---|---|---|---|---|
| Asthenia | 14 (60.9%) | 8 (34.8%) | 6 (26.1%) | |
| Nausea | 11 (47.8%) | 7 (30.4%) | 4 (17.4%) | |
| Diarrhea | 5 (21.7%) | 5 (21.7%) | | |
| Constipation | 3 (13.0%) | 3 (13.0%) | | |
| Oral dysesthesia | 4 (17.4%) | 3 (13.0%) | 1 (4.3%) | |
| Dysgeusia | 4 (17.4%) | 4 (17.4%) | | |
| Palmar-plantar erythrodysesthesia syndrome | 2 (8.7%) | 1 (4.3%) | 1 (4.3%) | |
| Paresthesia (neurotoxicity) | 7 (30.4%) | 1 (4.3%) | 6 (26.1%) | |
| Mucositis | 6 (26.1%) | 4 (17.4%) | | 2 (8.7%) |
| Erythema | 2 (8.7%) | 2 (8.7%) | | |
| Thyroiditis | 1 (4.3%) | 1 (4.3%) | | |
| Hepatitis | 1 (4.3%) | | | 1 (4.3%) |

Abbreviation: CIS-NIVO, cisplatin-nivolumab.

## Treatment efficacy

Treatment response obtained is depicted in Table S1.

No patients attained a complete response according to RECIST 1.1. Eight patients achieved a PR with an ORR of 34.8% [95% CI, 15.3%-54.2%]; 4 (17.4%) had a SD, and 11 (47.8%) had a PD as the best response to treatment. A clinical benefit was obtained in 12 patients (52.2%) (Figure 1A).

Nine patients maintained the SD or response for 6 months, resulting in a DCR after 6 months of 39.1% [95% CI, 19.7%-61.5%] (Figure 1B).

The 3 patients with Cushing's syndrome despite ongoing mitotane therapy promptly started metyrapone treatment before and during cisplatin and nivolumab. Of these, 2 exhibited disease progression as their best response and subsequently died, while 1 patient achieved a partial response.

Notably, a patient had a dramatic response (68% reduction in overall tumor size according to RECIST 1.1 criteria and 90% reduction of the hepatic target lesion) after cisplatin plus nivolumab. The therapy continued for the planned duration of 2 years without any signs of progression, and the disease was free from progression at the last follow-up, 28 months after the beginning of treatment (Figure S1). This patient had previously experienced recurrence of the disease to the liver after only 6 months after surgery despite receiving adjuvant mitotane and chemotherapy (cisplatin plus etoposide). Moreover, first-line chemotherapy with EDP-M, second-line therapy with temozolomide, and third-line with gemcitabine plus capecitabine for advanced disease were totally ineffective.

Fifteen patients underwent disease progression, and the median PFS was 4.3 months [95% CI, 3.9-13.0] (Figure 2A). Six patients died, and the median OS was 18.9 months [95% CI, 15.8-not reached] (Figure 2B).

Four patients were addressed to cytoreductive surgery after chemo–immunotherapy, and 3 of them were currently free from progression after 3, 3, and 7 months, respectively. The remaining patient underwent lung and liver progression after 7 months. Interestingly, 1 of these patients before starting chemo–immunotherapy had a large pelvic mass that was associated with abdominal ascites, which needed frequent evacuative paracentesis. The restaging CT scan showed a progression of pelvic mass after 8 cycles of therapy, despite an increase in the necrotic component. However, the ascites had disappeared completely, so the patient could be radically resected of the voluminous pelvic mass (Figure S2).

Moreover, 1 patient was given locoregional treatments on metastatic lesions after oligo disease progression after 22 treatment cycles, which were liver transarterial chemoembolization (TACE) and muscle metastasis cryoablation.

The 6-month interval after the end of a previous treatment with a cisplatin-containing regimen is regarded as a valuable cut-off to detect malignancies that may be sensitive to a cisplatin rechallenge.[21] To explore the potential contribution of cisplatin rechallenge to the efficacy of cisplatin + nivolumab immunochemotherapy, we assessed the patients' outcome by stratifying them based on the 6-month cut-off from the end of EDP-M to the beginning of cisplatin + nivolumab. No difference was found between the 2 groups in terms of either PFS and OS (Figure S3).

# Discussion

This retrospective single-center study showed that a chemo–immunotherapy combination with cisplatin plus nivolumab, administered as a second/third line in patients with metastatic ACC was active. The ORR of 35% and clinical benefit obtained in 52% of patients were relevant as they appeared superior to the results obtained by chemotherapy, target therapy, and immunotherapy alone administered in the same setting.[6-14] In addition, the response was durable since 39% of patients were free from progression after 6 months. In particular, a patient has achieved remarkable tumor shrinkage after a few months of therapy. He completed the maximum expected 2-year duration of chemo–immunotherapy without developing progression and was still free from progression after 6 months of treatment interruption. Because the disease was resistant to 2 previous lines of treatment for advanced disease, the result obtained with cisplatin and nivolumab in this patient was extraordinary. It is known that patients with ACC may develop hypercortisolism, which can hinder the efficacy of immunotherapy.[16] In this study, 3

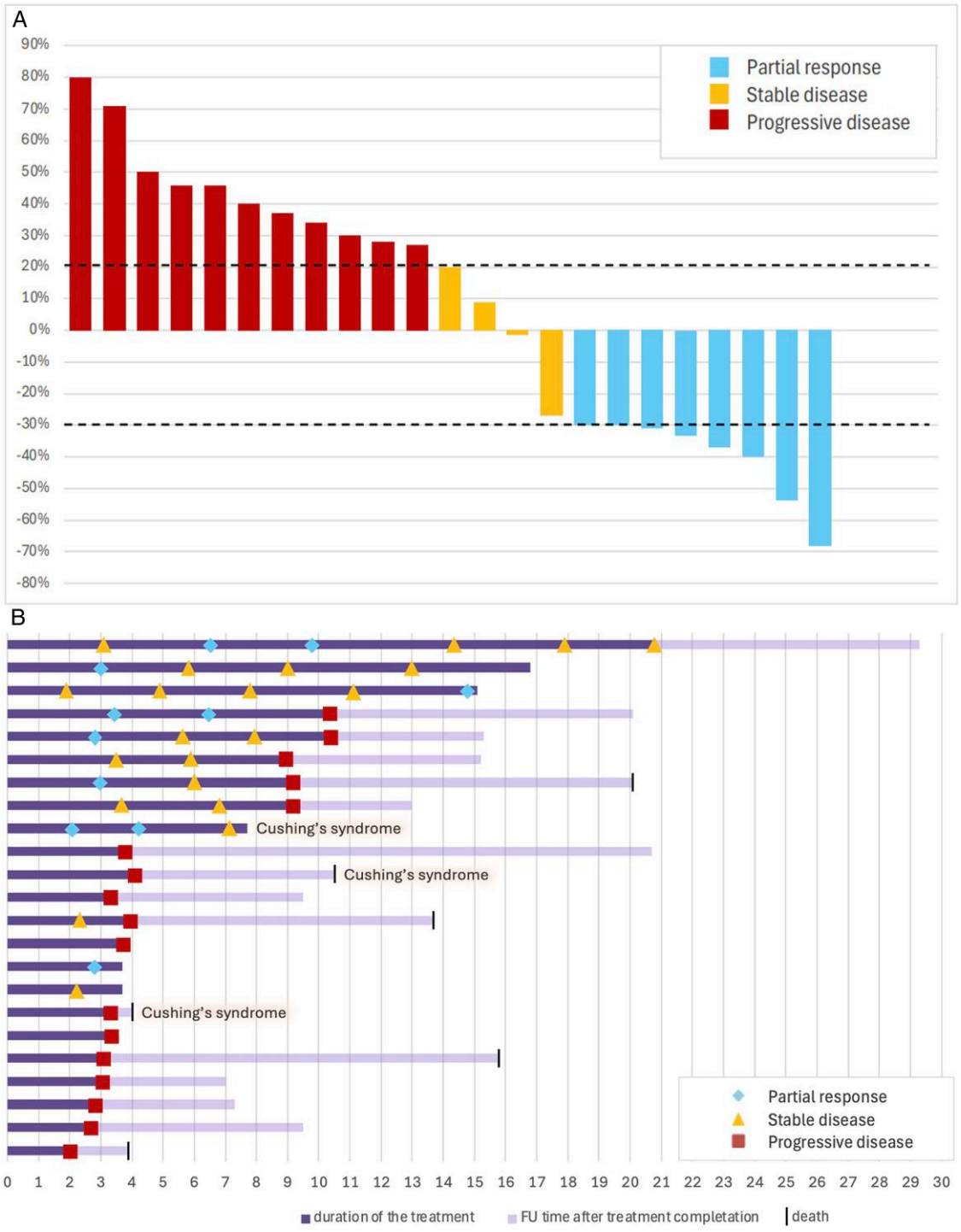


**Figure 1** (A) Waterfall plot illustrating clinical responses to combination therapy with cisplatin and nivolumab. The waterfall plot shows the best percentage change in target lesions. (B) Swimmer plot depicting treatment duration and follow-up times. The graph highlights cases of durable response and progression after initial benefit.

patients developed Cushing's syndrome despite being on mitotane therapy. They were immediately treated with full doses of metyrapone; 2 of them had a disease progression as the best response and subsequently died, while 1 had a partial response to therapy. These results indicate that Cushing's syndrome may not be a deterrent to immunotherapy due to the availability of powerful steroidogenesis inhibitors such as metyrapone.[22]

Overall, the median PFS of 4.3 months of patients included in this study was relatively short, although it was superior to that obtained by immunotherapy administered alone. However, the most significant result of this study was the relatively low proportion of death after a median follow-up of 15 months. Although during the study course 15 patients underwent progression, only 6 of them died, so the median OS was about 19 months.

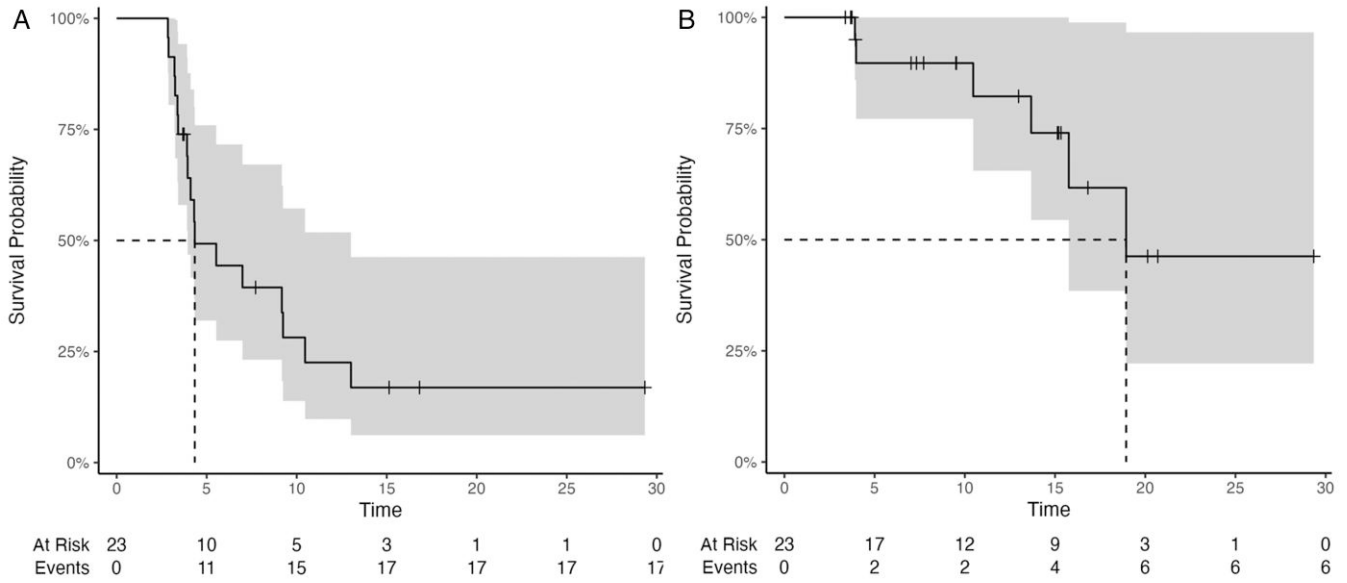


**Figure 2** (A) Progression-free survival curve. Median PFS, 4.34 (3.94-13.0). (B) Overall survival curve. Median OS, 18.9 (15.8-Inf). PFS, progression-free survival; OS, overall survival.

This study's survival data is of great interest because it is not only much better than the survival achieved with chemotherapy and target therapy administered as a second line in patients with metastatic ACC[6-13] but appears superior to the median survival of 14 months obtained with EDP-M in the first metastatic line.[5] These data suggest that the combination cisplatin plus nivolumab was efficacious, and the efficacy seems to be maintained beyond progression. After disease progression to cisplatin and nivolumab, 3 patients underwent debulking surgery, but they did not experience any further progression after 3, 3, and 7 months, respectively. Notably, 1 of these patients had a pelvic lesion, which increased in size after treatment; however, the mass was associated with ascites, which disappeared after chemo–immunotherapy allowing surgery feasible despite disease progression according to RECST 1.1 criteria. Therefore, in this patient, the overall response has been progression, but the disappearance of ascites that made surgery feasible identifies a favorable result of chemo–immunotherapy. Another patient received local regional therapies for oligoprogression, and the disease did not further progress after 7 months. Taken together, these data suggest that this regimen may have made the disease more indolent, leading to a positive effect on OS.

Disparities between PFS and OS have already been observed in immunotherapy studies that involved patients with metastatic disease from other histologies.[23,24]

It is noteworthy that the survival of patients enrolled in this study is higher than the 14 months of survival obtained with immunotherapy alone. Although this observation, which is based on an indirect comparison, should be taken with caution, these data suggest that the combination with chemotherapy may improve the efficacy of immunotherapy, as demonstrated in other neoplasms.[18,19]

In general, the present study's results indicate that combining an immune check point inhibitor with another antineoplastic drug is a way for overcoming the intrinsic immunoresistance of ACC. Along with the results obtained in renal cell carcinoma with the combination of immunotherapy and an antiangiogenetic drug, a prospective phase II study conducted in China tested the combination of camrelizumab and apatinib as second line in 21 patients with advanced ACC. The results were exceptionally good with objective remission rates of 53%, a 13-month PFS, and a 21-month OS.[25] Recently, a study conducted across multiple centers in Spain has published the results of a combination of atezolizumab (a PDL-1 inhibitor) and cabozantinib in 24 patients with pretreated advanced ACC. The ORRs (8%), mPFS (2.9 months), and mOS (13.5 months) did not appear to be better than what was expected solely from immunotherapy.[26] Based on these conflicting results, the efficacy of combining immunotherapy with antiangiogenetic drugs requires confirmation.

Overall, cisplatin plus nivolumab treatment was well tolerated, and there was no unexpected toxicity compared to what is commonly observed with the administration of the 2 individual drugs. Certainly, the administration of cisplatin is encumbered by neuropathy, which is related to the cumulative dose administered. This is why, in 6 nonprogressing patients requiring prolonged therapy, cisplatin was discontinued and treatment continued with nivolumab only. Immunotherapy resulted in the discontinuation of only 1 patient due to autoimmune hepatitis. The reason why cisplatin was chosen as the cytotoxic drug to be combined with nivolumab is that it is the most effective chemotherapy for treating ACC. Rechallenging cisplatin-containing regimens in patients who have been treated with EDP-M has been demonstrated to recruit disease responses.[27] Therefore, we could not exclude that some of the positive results obtained in this study may be attributable to the efficacy of cisplatin rechallenge, especially when a long time has elapsed since the administration of EDP-M.

However, the absence of an advantage in terms of PFS and OS of the group of patients with platinum-free interval greater than 6 months compared to their counterpart suggests that platinum resistance did not have a detrimental contribution on the efficacy of the combination regimen.

The strength of this study is that the patients enrolled were consecutive and all managed in a single reference center for this very rare disease. The retrospective nature is the main limitation.

In conclusion, the results of this study show that the combination of chemotherapy with immunotherapy is efficacious in the management of patients with metastatic ACC and has the potentiality to become the standard second-line therapy. These data need to be confirmed in a prospective study.

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## Authors' contributions

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## Supplementary material

Supplementary material is available at *European Journal of Endocrinology* online.

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## References

1. Fassnacht M, Assie G, Baudin E, et al.; ESMO Guidelines Committee. Adrenocortical carcinomas and malignant phaeochromocytomas: ESMO-EURACAN clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2020;31(11):1476-1490. https://doi.org/10.1016/j.annonc.2020.08.2099
2. Terzolo M, Daffara F, Ardito A, et al. Management of adrenal cancer: a 2013 update. *J Endocrinol Invest*. 2014;37(3):207-217. https://doi.org/10.1007/s40618-013-0049-2
3. Berruti A, Terzolo M, Sperone P, et al. Etoposide, doxorubicin and cisplatin plus mitotane in the treatment of advanced adrenocortical carcinoma: a large prospective phase II trial. *Endocr Relat Cancer*. 2005;12(3):657-666. https://doi.org/10.1677/erc.1.01025
4. Laganà M, Grisanti S, Cosentini D, et al. Efficacy of the EDP-M scheme plus adjunctive surgery in the management of patients with advanced adrenocortical carcinoma: the Brescia experience. *Cancers (Basel)*. 2020;12(4):941. https://doi.org/10.3390/cancers12040941
5. Fassnacht M, Terzolo M, Allolio B, et al.; FIRM-ACT Study Group. Combination chemotherapy in advanced adrenocortical carcinoma. *N Engl J Med*. 2012;366(23):2189-2197. https://doi.org/10.1056/NEJMoa1200966
6. Grisanti S, Cosentini D, Laganà M, et al. Clinical prognostic factors in patients with metastatic adrenocortical carcinoma treated with second line gemcitabine plus capecitabine chemotherapy. *Front Endocrinol (Lausanne)*. 2021;12:624102. https://doi.org/10.3389/fendo.2021.624102
7. Cosentini D, Badalamenti G, Grisanti S, et al. Activity and safety of temozolomide in advanced adrenocortical carcinoma patients. *Eur J Endocrinol*. 2019;181(6):681-689. https://doi.org/10.1530/EJE-19-0570
8. Laganà M, Grisanti S, Ambrosini R, et al. Phase II study of cabazitaxel as second-third line treatment in patients with metastatic adrenocortical carcinoma. *ESMO Open*. 2022;7(2):100422. https://doi.org/10.1016/j.esmoop.2022.100422
9. Kroiss M, Quinkler M, Johanssen S, et al. Sunitinib in refractory adrenocortical carcinoma: a phase II, single-arm, open-label trial. *J Clin Endocrinol Metab*. 2012;97(10):3495-3503. https://doi.org/10.1210/jc.2012-1419
10. O'Sullivan C, Edgerly M, et al. The VEGF inhibitor axitinib has limited effectiveness as a therapy for adrenocortical cancer. *J Clin Endocrinol Metab*. 2014;99(4):1291-1297. https://doi.org/10.1210/jc.2013-2298
11. Fassnacht M, Berruti A, Baudin E, et al. Linsitinib (OSI-906) versus placebo for patients with locally advanced or metastatic adrenocortical carcinoma: a double-blind, randomised, phase 3 study. *Lancet Oncol*. 2015;16(4):426-435. https://doi.org/10.1016/S1470-2045(15)70081-1
12. Haluska P, Worden F, Olmos D, et al. Safety, tolerability, and pharmacokinetics of the anti-IGF-1R monoclonal antibody figitumumab in patients with refractory adrenocortical carcinoma. *Cancer Chemother Pharmacol*. 2010;65(4):765-773. https://doi.org/10.1007/s00280-009-1083-9
13. Naing A, Lorusso P, Fu S, et al. Insulin growth factor receptor (IGF-1R) antibody cixutumumab combined with the mTOR inhibitor temsirolimus in patients with metastatic

adrenocortical carcinoma. *Br J Cancer*. 2013;108(4):826-830. https://doi.org/10.1038/bjc.2013.46
14. Campbell MT, Balderrama-Brondani V, Jimenez C, et al. Cabozantinib monotherapy for advanced adrenocortical carcinoma: a single-arm, phase 2 trial. *Lancet Oncol*. 2024;25(5):649-657. https://doi.org/10.1016/S1470-2045(24)00095-0
15. Ababneh O, Ghazou A, Alawajneh M, et al. The efficacy and safety of immune checkpoint inhibitors in adrenocortical carcinoma: a systematic review and meta-analysis. *Cancers (Basel)*. 2024;16(5):900. https://doi.org/10.3390/cancers16050900
16. Grisanti S, Cosentini D, Laganà M, et al. The long and winding road to effective immunotherapy in patients with adrenocortical carcinoma. *Future Oncol*. 2020;16(36):3017-3020. https://doi.org/10.2217/fon-2020-0686
17. Kaplon H. Translational learnings in the development of chemo-immunotherapy combination to bypass the cold tumor microenvironment in pancreatic ductal adenocarcinoma. *Front Oncol*. 2022;12:835502. https://doi.org/10.3389/fonc.2022.835502
18. Garassino MC, Gadgeel S, Speranza G, et al. Pembrolizumab plus pemetrexed and platinum in nonsquamous non-small-cell lung cancer: 5-year outcomes from the phase 3 KEYNOTE-189 study. *J Clin Oncol*. 2023;41(11):1992-1998. https://doi.org/10.1200/JCO.22.01989
19. Liu SV, Reck M, Mansfield AS, et al. Updated overall survival and PD-L1 subgroup analysis of patients with extensive-stage small-cell lung cancer treated with atezolizumab, carboplatin, and etoposide (IMpower133). *J Clin Oncol*. 2021;39(6):619-630. https://doi.org/10.1200/JCO.20.01055
20. Ambrosini R, Balli MC, Laganà M, et al. Adrenocortical carcinoma and CT assessment of therapy response: the value of combining multiple criteria. *Cancers (Basel)*. 2020;12(6):1395. https://doi.org/10.3390/cancers12061395
21. Wilson MK, Pujade-Lauraine E, Aoki D, et al. Participants of the fifth ovarian cancer consensus conference. Fifth ovarian cancer consensus conference of the gynecologic cancer InterGroup: recurrent disease. *Ann Oncol*. 2017;28(4):727-732. https://doi.org/10.1093/annonc/mdw663
22. Claps M, Cerri S, Grisanti S, et al. Adding metyrapone to chemotherapy plus mitotane for Cushing's syndrome due to advanced adrenocortical carcinoma. *Endocrine*. 2018;61(1):169-172. https://doi.org/10.1007/s12020-017-1428-9
23. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med*. 2015;373(2):123-135. https://doi.org/10.1056/NEJMoa1504627
24. Herbst RS, Garon EB, Kim DW, et al. Five year survival update from KEYNOTE-010: pembrolizumab versus docetaxel for previously treated, programmed death-ligand 1-positive advanced NSCLC. *J Thorac Oncol*. 2021;16(10):1718-1732. https://doi.org/10.1016/j.jtho.2021.05.001
25. Zhu YC, Wei ZG, Wang JJ, et al. Camrelizumab plus apatinib for previously treated advanced adrenocortical carcinoma: a single-arm phase 2 trial. *Nat Commun*. 2024;15(1):10371. https://doi.org/10.1038/s41467-024-54661-9
26. Capdevila J, Hernando J, Molina-Cerrillo J, et al. Cabozantinib plus atezolizumab in advanced, progressive endocrine malignancies: a multi-cohort, basket, phase II trial (CABATEN/GETNE-T1914). *Clin Cancer Res*. 2025;31(22):4655-4663. https://doi.org/10.1158/1078-0432.CCR-25-2143
27. Zhulikov YA, Kovalenko EI, Artamonova E, et al. Reintroduction of platinum-based chemotherapy ± mitotane for advanced adrenocortical cancer: single-center retrospective trial. *ESMO Open*. 2025;10:104355. https://doi.org/10.1016/j.esmoop.2025.104355