



Original Research

Outcome of adrenocortical carcinoma patients included in early phase clinical trials: Results from the French network ENDOCAN-COMETE



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Abstract Background: At metastatic stage, treatment of adrenocortical carcinoma (ACC) relies in first line on mitotane therapy, combination of mitotane with locoregional therapies or cisplatin-based chemotherapy according to initial presentation. In second line, ESMO-EURACAN recommendations favour enrolment of patients in clinical trials investigating experimental therapies. However, the benefit of this approach remains unknown. **Methods:** The aim of our retrospective study was to analyse the inclusion and outcomes of all patients of the French cohort ENDOCAN-COMETE included in early clinical trials between 2009 and 2019.

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Results: Of the 141 patients for whom a local or national multidisciplinary tumour board recommended, as first choice, to look for clinical trial, 27 patients (19%) were enrolled in 30 early clinical trials. Median progression-free survival (PFS) was 3.02 months (95% confidence interval [95% CI]; 2.3–4.6) and median overall survival (OS) was 10.2 months (95% CI; 7.13–16.3) while the best response, evaluable in 28 of 30 trial participants according to RECIST 1.1 criteria, was partial response for 3 patients (11%) stable disease for 14 patients (50%) and progressive disease for 11 patients (39%), resulting in a disease control rate of 61%. Median growth modulation index (GMI) in our cohort was 1.32, with a significantly prolonged PFS in 52% of the patients compared to the previous line. The Royal Marsden Hospital (RMH) prognostic score was not associated with OS in this cohort.

Conclusion: Our study suggests that patients with metastatic ACC benefit from inclusion in early clinical trials in second line. As recommended, if a clinical trial is available, it should be the first choice for suitable patients.

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1. Introduction

Adrenocortical carcinoma (ACC), a rare cancer originating from the adrenal cortex has a poor prognosis with up to 50% of metastatic stage at initial diagnosis and when localised, a high risk of recurrence [1–3]. The median overall survival (OS) of metastatic ACC patients varies between 10 and 21 months with a 5-year survival of around 10% [1]. Current recommendations for the treatment of ACC patients are mainly based on retrospective and single-arm phase II studies and only two phase III trials [1]. Surgery remains the only curative treatment modality for localised disease. At metastatic stage, treatment relies in first line on mitotane therapy, combination of mitotane with locoregional therapies or cisplatin-based chemotherapy according to initial presentation [4,5]. The first randomised phase III trial ever performed in ACC patients, the FIRMACT study, have shown improved median progression-free survival (PFS) of 5 months and a disease control rate (DCR) of 58.3% with Mitotane-Etoposide-Doxorubicin-Platinum (MEDP), as compared to Mitotane-Streptozocin (DCR of 31.4%) [6]. Other drugs and drug combinations have been tested in advanced ACC but none has emerged as promising based on absence of confirmed partial response rate above 15% and or median PFS above 6 months [7,8]. The second randomised trial in ACC compared linsitinib to placebo and was negative [9] while several tyrosine kinase inhibitors (TKI) have been investigated in advanced ACC with largely disappointing results [10–12]. Median PFS were 4 and 2.2 months with gemcitabine + capecitabine or streptozocin + mitotane respectively and DCR of 29.9% and 31.4% [6,8]. More recently, temozolomide and cabazitaxel did not improve the prognostic of patients with median PFS of 3.5 months (DCR of 35.8%) and 1.5 months (DCR of 24%) respectively [13,14]. In addition, a dedicated challenge in metastatic ACC patients is drug-drug interaction due to mitotane-induced CYP3A4 activity [15].

In recent recommendations, after first line failure, experts favour enrolment of patients in clinical trials investigating experimental therapies including phase I trials [4,5]. However, the percentage of patients able to

benefit from such an approach as well as real benefits remain unknown. Therefore, the aim of our retrospective study was to analyse the inclusion and outcomes of all patients of the French cohort ENDOCAN-COMETE included in early clinical trials between 2009 and 2019, when access to next-generation sequencing (NGS) evaluation in routine was limited.

2. Patients and methods

2.1. Study population

The medical files of metastatic ACC patients followed up between January 2009 and December 2019 were reviewed in all centres of the French network ENDOCAN-COMETE. Patients enrolled in one or more phase I or II clinical trials were included in this study. Clinical data were entered by each centre and then reviewed by one investigator (P.D.R.). Informed consent was obtained from all patients, and the study was approved by each local ethical committee.

The following parameters were recorded at the time of initial diagnosis: gender, ECOG Performance Status, side and size of the primary tumour, hormonal secretion excess, Ki67 index, WEISS score, ENSAT stage, and mENSAT-GRAS criteria (mENSAT TNM classification combined with GRAS parameters: Grade defined by Weiss score below or above 6 or Ki-67 below or above 20%; resection status of the primary; age below or above 50 years; tumour- or hormone-related symptoms) [3]. The management of each patient has been reviewed: surgical resection quality, local and adjuvant measures, time between diagnosis and metastatic stage and treatments for metastatic disease with response and PFS.

The following parameters were recorded at the time of inclusion in early clinical trial: age, ECOG Performance Status, Royal Marsden Hospital score (RMH score; LDH normal (0) versus LDH > UNL (+1), albumin > 35 g/l (0) versus albumin < 35 g/l (+1), site of metastasis < 2 (0) versus > 2 (+1) [16], PFS

measured with for the last prior therapeutic line and during the early clinical trial.

2.2. Statistical analysis

Data were summarised by count and percentage for categorical variables and by mean with standard deviation or median with range for continuous variables. Missing data were excluded for percentage calculations. PFS was defined as the time from the start of each line to the date of disease progression, or death from any cause. OS was measured from the start of early phase clinical trial to death. The Kaplan-Meier method was used to estimate survival end-points (OS and PFS). The hazard ratio and associated 95% confidence interval (CI) were calculated using a Cox proportional-hazards model. All statistical analyses were performed using R software® (version 4.1.1).

3. Results

3.1. Patient's baseline characteristics

Between 2009 and 2019, a local or national multi-disciplinary tumour board recommended, as first choice, to look for clinical trial for 141 patients. Of them, 27 patients (19%) were enrolled in 30 early clinical trial and therefore included in our study. Other patients did not access to trial for two main reasons: they were not suitable for early clinical trial or no trial was available. The clinical and pathological characteristics of the 27 patients at diagnosis are summarised in Table 1. All patients were characterised according to mENSAT-GRAS criteria including 6 (22%) patients aged over 50 years and 20 (74%) patients with hormonal secretion excess at initial diagnosis. ENSAT stage at initial diagnosis was I–III in 41% of cases and mean size of the primary was 131 millimetres. Ki67 index was equal or higher than 20% in 19 patients (70%) cases. Patients with metachronous metastatic disease had a mean time from localised to metastatic disease of 10 months (range 1.1–81.8 months).

Table 1
Characteristics of patients at initial diagnosis.

Variable	n
Total (%)	27 (100)
Sex = male (%)	9 (33.3)
Age (mean (SD))	39.3 (13.5)
ENSAT stage (%)	
2	4 (16.7)
3	6 (25.0)
4	14 (58.3)
Size of primary (mm) (mean (SD))	131.1 (46.1)
Ki67 (mean (SD))	35.8 (22.6)
Primary tumour resection = yes (%)	26 (96.3)
Resection status = R1 (%)	6 (22.2)
Hormonal secretion = yes (%)	20 (74)

Table 2
Characteristics of patients at inclusion.

Variable	n
Total (%)	30 (100)
Mean age (SD)	41.6 (12.3)
ECOG Performance status = 0–1 (%)	30 (100)
RMH Score (%)	
0	7 (26.9)
1	5 (19.2)
2	8 (30.8)
3	6 (23.1)
Number of previous lines (median (range))	2 (0–4)
Previous locoregional therapy = yes (%)	20 (87)
PFS of prior line (median)	3.0 months

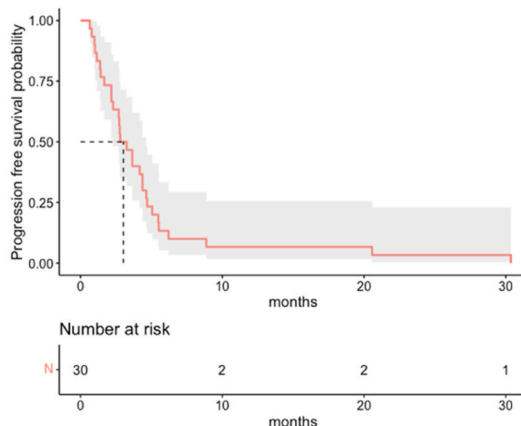
3.2. Early phase clinical trial inclusion

Of the 27 patients included in our cohort, 25 participated in one trial, 1 patient in two trials and 1 patient in three trials; therefore, 30 inclusions were studied. The characteristics of the patients at inclusion are summarised in Table 2. All patients had an ECOG performance status of 0/1, which was an inclusion criteria in trials. The RMH score was 0, 1, 2 or 3 in 7 (27%), 5 (19%), 8 (31%) and 6 (23%) patients respectively with one missing. Patients received a median of two previous systemic lines of therapy, mostly cisplatin-based chemotherapy (25/27; 93%). Only one patient participated in a trial in first line while the patient who participated in two trials was included in second and third line and the one who participated in three trials was included in second, third and fourth line. Twenty of 23 had locoregional treatments. Median PFS obtained in 27/30 patients during the last systemic treatment prior to the inclusion was 3.0 months (95% CI; 2–5.72).

3.3. Tumour responses and survival analysis

Overall, 28 trial participants were evaluable for outcomes analysis. One patient was excluded for toxicity before the first tumour assessment, and one patient withdrew his consent. During early phase clinical trial median PFS was 3.02 months (95% CI; 2.3–4.6) (Fig. 1A), and median OS was 10.2 months (95% CI; 7.13–16.3) (Fig. 1B). The best response was evaluable in 28 of 30 trial participants according to RECIST 1.1 criteria. Three patients (11%) achieved a partial response, 14 (50%) patients had a stable disease and 11 (39%) patients had a progressive disease, resulting in a DCR of 61%. The median time to best response was 1.3 months (range 0.7 to 6.9). Details about treatment-related best responses are shown in Table 3. Two of the PR were obtained with an anti-PDL1 antibody and one with a combination of gemcitabine + anti-EGFR + anti-IGF1-R. Molecular alterations did not drive the enrolment of these three patients. Stable diseases were observed with a variety of molecules.

A. Progression free survival



B. Overall survival (survival status was unavailable for 3 patients)

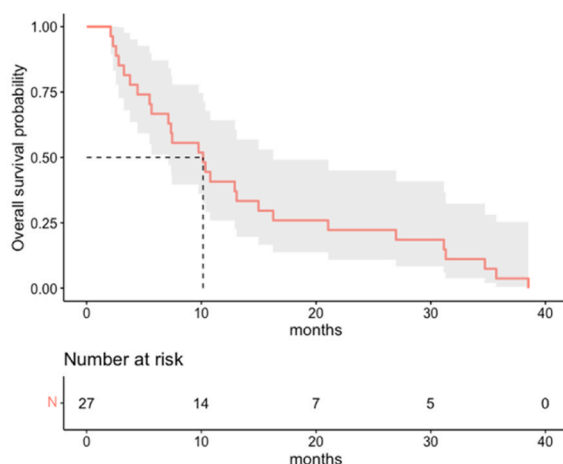


Fig. 1. Survival analysis during early phase clinical trial.

3.4. Growth modulation index

The retrospective nature of the cohort and the large variety of molecules studied induce obvious biases in the analysis. Therefore, we assessed the clinical benefit of the strategy by using each patient as his/her own control using the previously published growth modulation index (GMI), that is, the ratio of two consecutive PFSs [17]. A GMI exceeding 1.3 suggests a clinical benefit as the second treatment prolonged the PFS achieved with the previous treatment by at least 30%. GMI was evaluable in 27/30 patients. Median GMI in our cohort was 1.32 (Fig. 2). Fourteen patients (52%) had a GMI > 1.3.

3.5. Prognostic role of the RMH score

The RMH prognostic score is associated with OS for many tumour types and represents a helpful tool in evaluating the eligibility of patients into phase I trials but was never validated for ACC [18]. RMH was

evaluable in 26 patients. Twelve patients had a RMH score ≤ 1 and 14 patients had a RMH ≥ 2 . Median PFS was 2.79 and 2.77 months ($p = 0.56$), respectively. Median OS was 9.95 months (95% CI; 7.36 to NA) and 8.0 months (95% CI; 3.78–27), respectively ($p = 0.56$) (Fig. 3). No statistical difference in PFS and OS was found between the two groups.

4. Discussion

In recent guidelines from both ESMO-EURACAN and ESE-ENSAT, it is recommended to include suitable patients in clinical trials in second line [4,5]. However, to the best of our knowledge, the feasibility and benefit of these inclusions have never been reported before. Therefore, the aim of our study was to describe the inclusions in early clinical trials of patients with metastatic ACCs and followed within the French network EN-DOCAN-COMETE between 2009 and 2019 as one of the major objectives of the trial.

Table 3
Treatment and responses.

Patient	Trial acronym	Molecule	Target	Best response
#1	JAVELIN	Avelumab	PDL1	PR
#2	JAVELIN	Avelumab	PDL1	SD
#3	JAVELIN	Avelumab	PDL1	PD
#4	JAVELIN	Avelumab	PDL1	PD
#5	JAVELIN	Avelumab	PDL1	PR
#6	JAVELIN	Avelumab	PDL1	SD
#7	JAVELIN	Avelumab	PDL1	PD
#8	JAVELIN	Avelumab	PDL1	SD
#8	C12-315-03/LYTIX	LTX-315	PDL1	SD
#9	JAVELIN	Avelumab	PDL1	SD
#10	JAVELIN	Avelumab	PDL1	PD
#11	APL-A-010-08	Plitidepsine + Gemcitabine	Didemnines + chemotherapy	PD
#12	I6F-MC-JJCD	LY303947	NOTCH	not available
#13	EZH117208	GSK2816126	EZH2	PD
#14	GSK204653	GSK3326595	PRMT5	SD
#15	W00101 IV 1 01	W0101	IGF-1R	PD
#16	BAY1000394/14484	Roniciclib	CDK1/2/4	not available
#17	PRIMO	Nivolumab + Ipilimumab IV + Tilsotolimod IT	PD1 + CTLA4 + TLR9	SD
#18	TAS-120-202	TAS120	FGFR	SD
#18	PM14-A-001-17	PM14	RNA synthesis inhibitor	PD
#18	OSE144301	BI765063	SIRP α -R	PD
#19	I8J-MC-JYCA	LY3300054	PDL1	SD
#20	NMS-CDCA-354	NMS-1116354	CDC7	SD
#21	BP29392	Atezolizumab + RO7009789	PDL1 + CD40	SD
#22	AG270-C-001	AG270	MAT2A	SD
#23	AVE1642	Gemcitabine + Erlotinib + AVE1642	EGFR + IGF-1R + chemotherapy	PR
#24	JAVELIN	Avelumab	PDL1	SD
#25	PACIFIK	cisplatin + pazopanib	VEGFR1-3 + chemotherapy	SD
#26	JAVELIN	Avelumab	PDL1	PD
#27	W00101IV101	W0101	IGF-1R	PD

PR: partial response; SD: stable disease; PD: progressive disease.

Of 141 patients for whom a local or national multi-disciplinary tumour board recommended to look for a suitable clinical trial, 27 patients (19%) were included in 30 early clinical trials. Other patients did not access to trial for two main reasons: they were not suitable for

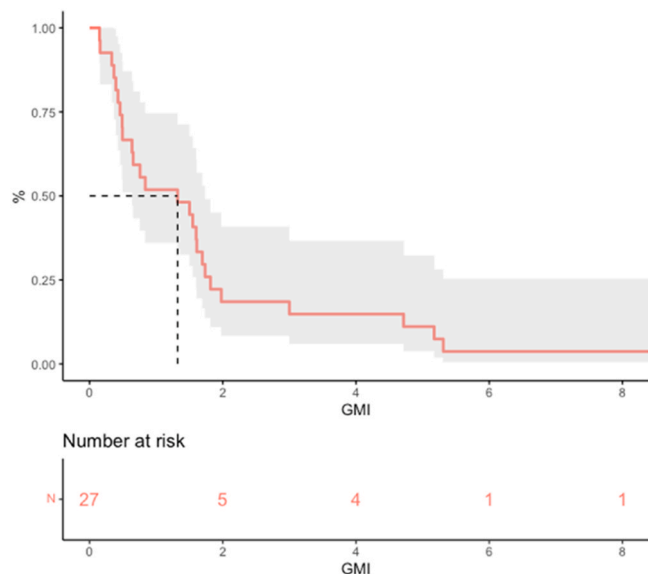


Fig. 2. Growth modulation index distribution.

early clinical trial or no trial was available. Despite patients with rare cancer benefit from network like the French network ENDOCAN-COMETE that offer national tumour board with experts, the feasibility of enrolment of rare cancer in early phase trials faces multiple challenges. It includes competition with most frequent cancers, specific basket trials with cohorts of certain types of cancer and complex molecular targets. In this study including patients between 2009 and 2019, access to molecular characterisation of the tumour was not yet routinely available. A period effect may also explain the low inclusion rate of patients.

In our cohort, the median PFS was 3.02 months and the median OS was 10.2 months with a DCR of 61%. Alternative second lines are disappointing in ACC. PFS results in our study are modest but the DCR was higher than expected which may be related to appropriate selection of patients for trials. Indeed, in our study, patients are selected to be suitable for phase I/II clinical trials, thus 100% of them had a performance status of 0 or 1. Our cohort does not represent most ACC patients and therefore prone to a selection bias that prevents us from comparing with other second lines in ACC. Moreover, factors of good prognosis such as median age of 41.6 years, prolonged disease free interval in some patients with metachronous metastasis and median OS

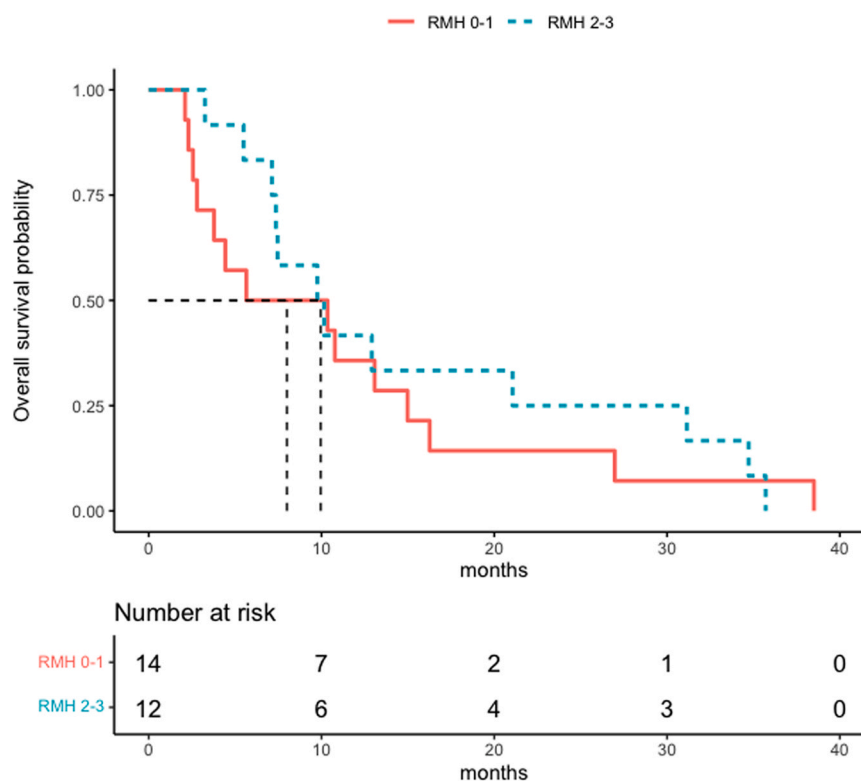


Fig. 3. Overall survival with early phase clinical trial according to RMH score at inclusion.

from metastatic diagnosis of more than 40 months suggest a cohort that behaves as long survivors as previously described [19]. These patients could be long responders. Some of them have been included in the JAVELIN study, a phase Ib study with avelumab [20]. In the JAVELIN study, 50 patients with metastatic ACC were included, the median DCR was 48%, and the median PFS of 2.6 months but with prolonged disease control in some patients. Of note, in our cohort, only one of the two partial responders to Avelumab and one of the five patients with stable disease received concomitant mitotane. The third patient who experienced a partial response under an association of gemcitabine + erlotinib + an IGF1-R inhibitor did not either receive concomitant mitotane.

To avoid this bias and determine the clear clinical benefit for these patients, we evaluated the GMI. By evaluating each patient as his own control, the use of GMI overcomes the heterogeneity of treatments used. GMI calculation showed a significantly prolonged PFS in 52% of the patients as compared to the previous line. This result strongly supports offering patients with recurrent disease inclusion in clinical trial, and for instance early phase.

Limits of our study are its retrospective character. Statistical analyses were limited by the small size of the sample, especially for the RMH score.

To conclude, our study suggests that patients with metastatic ACC may benefit from inclusion in early

clinical trials in second line. As recommended, if a clinical trial is available, it should be the first choice for suitable patients given that access to early clinical trial for rare cancer should be improved.

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CRedit authorship contribution statement

Ségolène Hescot: Conceptualisation, Supervision, Writing – original draft. **Véronique Debien:** Data curation. **Julien Hadoux:** Investigation, Writing – review & editing. **Delphine Drui:** Data curation. **Magalie Haissaguerre:** Data curation. **Christelle de la Fouchardiere:** Data curation. **Delphine Vezzosi:** Data curation. **Christine Do Cao:** Data curation. **Rossella Libé:** Writing – review & editing. **Christophe Le Tourneau:** Investigation, Conceptualisation. **Eric Baudin:** Investigation, Conceptualisation, Writing – review & editing. **Christophe Massard:** Investigation, Writing – review & editing. **Pauline du Rusquec:** Conceptualisation, Formal analysis.

Declaration of Competing Interest

The authors declare no conflict of interest.

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