

## ORIGINAL ARTICLE

## Combination Chemotherapy in Advanced Adrenocortical Carcinoma

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## ABSTRACT

**BACKGROUND**

Adrenocortical carcinoma is a rare cancer that has a poor response to cytotoxic treatment.

**METHODS**

We randomly assigned 304 patients with advanced adrenocortical carcinoma to receive mitotane plus either a combination of etoposide (100 mg per square meter of body-surface area on days 2 to 4), doxorubicin (40 mg per square meter on day 1), and cisplatin (40 mg per square meter on days 3 and 4) (EDP) every 4 weeks or streptozocin (streptozotocin) (1 g on days 1 to 5 in cycle 1; 2 g on day 1 in subsequent cycles) every 3 weeks. Patients with disease progression received the alternative regimen as second-line therapy. The primary end point was overall survival.

**RESULTS**

For first-line therapy, patients in the EDP-mitotane group had a significantly higher response rate than those in the streptozocin-mitotane group (23.2% vs. 9.2%,  $P<0.001$ ) and longer median progression-free survival (5.0 months vs. 2.1 months; hazard ratio, 0.55; 95% confidence interval [CI], 0.43 to 0.69;  $P<0.001$ ); there was no significant between-group difference in overall survival (14.8 months and 12.0 months, respectively; hazard ratio, 0.79; 95% CI, 0.61 to 1.02;  $P=0.07$ ). Among the 185 patients who received the alternative regimen as second-line therapy, the median duration of progression-free survival was 5.6 months in the EDP-mitotane group and 2.2 months in the streptozocin-mitotane group. Patients who did not receive the alternative second-line therapy had better overall survival with first-line EDP plus mitotane (17.1 month) than with streptozocin plus mitotane (4.7 months). Rates of serious adverse events did not differ significantly between treatments.

**CONCLUSIONS**

Rates of response and progression-free survival were significantly better with EDP plus mitotane than with streptozocin plus mitotane as first-line therapy, with similar rates of toxic events, although there was no significant difference in overall survival. (Funded by the Swedish Research Council and others; FIRM-ACT ClinicalTrials.gov number, NCT00094497.)

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\*Additional members of the First International Randomized Trial in Locally Advanced and Metastatic Adrenocortical Carcinoma Treatment (FIRM-ACT) study group are listed in the Supplementary Appendix, available at NEJM.org.

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**A**DRENOCORTICAL CARCINOMA IS A RARE cancer (estimated incidence, 0.7 to 2.0 cases per 1 million population per year)<sup>1,2</sup> with a poor prognosis; the 5-year survival rate is less than 15% among patients with metastatic disease.<sup>3-7</sup> Mitotane is the only drug approved for the treatment of adrenocortical carcinoma and is used both as adjuvant therapy and for advanced disease,<sup>8-14</sup> although its efficacy has never been shown in a randomized trial. The experience with other antineoplastic drugs for the treatment of this disease is even more limited. Current treatment strategies for advanced disease are based exclusively on retrospective series and small phase 2 trials.

During the International Consensus Conference on adrenocortical carcinoma in 2003,<sup>15</sup> the first randomized phase 3 trial of treatment for this rare tumor was planned. In this trial, called the First International Randomized Trial in Locally Advanced and Metastatic Adrenocortical Carcinoma Treatment (FIRM-ACT), we compared the two most successful regimens in patients with advanced disease. One regimen, which combined etoposide, doxorubicin, and cisplatin (EDP) with mitotane, had resulted in an objective response rate of 53% in a study involving 28 patients with advanced adrenocortical carcinoma.<sup>16</sup> The second regimen, which combined streptozocin with mitotane, had resulted in an objective response rate of 36% in a study involving 22 patients with advanced adrenocortical carcinoma.<sup>17</sup> The goal of the trial was to establish a treatment standard for advanced disease.

## METHODS

### PATIENTS

Eligibility criteria were an age of 18 years or older; histologically confirmed and radiologically measurable adrenocortical carcinoma that was not amenable to radical surgical resection; no previous treatment with cytotoxic drugs, except mitotane; an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 (0, asymptomatic; 1, symptomatic but ambulatory; and 2, symptomatic and in bed <50% of the day); adequate hematologic and biochemical function; and no history of another cancer. (Detailed inclusion and exclusion criteria are provided in Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org.)

### STUDY DESIGN

This study was an investigator-initiated, randomized, controlled, open-label, parallel-group trial that was conducted in 12 countries at 40 specialized centers for the treatment of adrenocortical carcinoma. After registration, patients were randomly assigned to receive either EDP plus mitotane or streptozocin (streptozotocin) plus mitotane with the use of concealed 1:1 randomization by the data center in Uppsala, Sweden. The technique of randomly permuted balanced blocks and random block size was used.

The trial conformed to the principles of the Declaration of Helsinki and the Good Clinical Practice Guidelines and was approved by the ethics committee at each study center. All patients provided written informed consent. An independent data and safety monitoring board supervised the collection of efficacy and safety data (board members are listed in the Supplementary Appendix).

The protocol committee and the study statistician designed the study and wrote the first draft of the manuscript; the final draft was approved by all the authors. (The protocol, with the statistical analysis plan, is available at NEJM.org.) In accordance with the regulations of European Medicines Agency, one institution was selected to be legally responsible for conducting the study, and Uppsala University Hospital accepted this role. The drugs were purchased through the regular health care plans of the patients. No commercial entity was involved in this trial. Data were collected at Uppsala University and statistically analyzed at the Universities of Marburg and Munich, Germany. All authors vouch for the accuracy of the data and the fidelity of the study to the protocol. Only investigators participating in the trial were involved in the design of the trial, the analysis of the data, and the writing of the manuscript. No one who is not an author contributed to the preparation of the manuscript.

On the basis of the results of the phase 2 trials,<sup>16,17</sup> we anticipated a high percentage of treatment failures during first-line therapy. Therefore, the protocol specified provision of second-line therapy with the alternative regimen for all patients who had either disease progression or unacceptable toxic events with the assigned regimen. Accordingly, two parallel phase 2 trials for second-line treatment were embedded in the study design.

**STUDY TREATMENT**

The EDP–mitotane regimen consisted of etoposide at a dose of 100 mg per square meter of body-surface area administered intravenously on days 2, 3, and 4 of each cycle; doxorubicin at a dose of 40 mg per square meter given intravenously on day 1; cisplatin at a dose of 40 mg per square meter given intravenously on days 3 and 4; and oral mitotane administered continuously. One cycle of the regimen was defined as a 4-week interval. The streptozocin–mitotane regimen consisted of streptozocin given intravenously at a dose of 1 g for 5 days in the first cycle and 2 g on day 1 in subsequent cycles, with continuous oral administration of mitotane. One cycle of the regimen was defined as a 3-week interval.

In both treatment schedules, mitotane was started a minimum of 1 week before the initiation of the cytotoxic treatment, with the goal of attaining a blood level of 14 to 20 mg per liter.<sup>8,9</sup> Since adjuvant mitotane therapy is frequently used in patients with adrenocortical carcinoma,<sup>10</sup> previous treatment with mitotane before study entry was allowed. Concomitant medications and therapies that were deemed to be necessary for the supportive care and safety of the patients were also allowed at the discretion of the local investigators. Glucocorticoid replacement was recommended in all patients except those with persistent Cushing's syndrome.

**STUDY ASSESSMENTS**

Patients were seen at the start of every treatment cycle for physical examination, determination of ECOG performance status, a complete blood count, and serum biochemical measurements. Tumor response, measured according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.0,<sup>18</sup> was assessed every 8 weeks by means of thoracic and abdominal computed tomography or magnetic resonance imaging (Text 1 in the Supplementary Appendix). We calculated overall survival and progression-free survival as the time from the date of randomization until the date of death and the date of disease progression, respectively. Death was recorded as related or not related to progressive adrenocortical carcinoma. Data for patients who survived and for those surviving without disease progression were censored at the date of the last follow-up visit and the date of the last tumor-response assessment, respectively. We assessed quality of life every 8 weeks using the European

Organization for Research and Treatment of Cancer (EORTC) quality-of-life core questionnaire (QLQ-C30, version 3.0).<sup>19</sup> Safety assessments were performed before each treatment cycle with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 2.0.<sup>19</sup> Expected toxic events were recorded only if they met established criteria for a serious adverse event.<sup>20</sup>

**END POINTS**

The primary end point was overall survival, and secondary end points were progression-free survival, tumor response, and quality of life. Secondary objectives were to explore the effect of a blood mitotane level of 14 to 20 mg per liter on the clinical outcome and to determine the response to each of the two regimens as second-line treatment.

**STATISTICAL ANALYSIS**

The trial was designed to have a power of 80% to detect a risk reduction of 33% in the EDP–mitotane group, as compared with the streptozocin–mitotane group. We determined that such an analysis would require the observation of up to 200 deaths on the basis of a two-sided group sequential log-rank test at a type I error level of 5%. All analyses were performed on an intention-to-treat basis. Overall survival and progression-free survival were analyzed with the use of the Kaplan–Meier method and compared between groups by means of the log-rank test. A Cox proportional-hazards model was used to estimate the hazard ratios. Rates of best overall tumor response to treatment were estimated, with 95% confidence intervals, by using the method of Clopper and Pearson and were compared by using exact methods for testing and estimating (e.g., Fisher's exact test and exact confidence intervals for odds ratios).

Serious adverse events were described according to the treatment period, with the omission of deaths from progression of adrenocortical carcinoma. The numbers of events per patient and per month of therapy were compared between treatment groups with the use of the exact Wilcoxon–Mann–Whitney test and Poisson-regression analysis, respectively. The global health score on the QLQ-C30 and the absolute change in the score from baseline were used as summary measures of the quality of life and were compared between

**Table 1. Baseline Characteristics in the Intention-to-Treat Population.\***

Characteristic	EDP-M (N=151)	Sz-M (N=153)
Age — yr		
Median	51.9	50.0
Range	19.0–76.2	18.8–72.8
Sex — no. (%)		
Male	60 (39.7)	61 (39.9)
Female	91 (60.3)	92 (60.1)
Tumor stage — no. (%)		
III	0	1 (0.7)
IV	151 (100.0)	152 (99.3)
Endocrine symptoms — no. (%)		
Cushing's syndrome with or without other symptoms	60 (39.7)	64 (41.8)
Conn's syndrome only	2 (1.3)	3 (2.0)
Virilization only	6 (4.0)	7 (4.6)
Feminization only	3 (2.0)	2 (1.3)
No symptoms	70 (46.4)	68 (44.4)
Missing data	10 (6.6)	9 (5.9)
ECOG performance status score — no. (%)		
0	73 (48.3)	72 (47.1)
1	64 (42.4)	60 (39.2)
2	13 (8.6)	21 (13.7)
4	1 (0.7)†	0
Time since primary diagnosis — mo‡		
Median	7.3	4.5
Range	0–183.7	0–111.6
No. of affected sites§		
Median	3	3
Range	1–7	1–8
Blood mitotane level		
No. of analyzed samples	130	136
Median — mg/liter	6.3	5.1
Range — mg/liter	0–33.0	0–56.0

\* There were no significant differences between groups, except as indicated. EDP-M denotes etoposide, doxorubicin, and cisplatin plus mitotane, and Sz-M streptozocin plus mitotane.

† In this patient, a score of 4 on the Eastern Cooperative Oncology Group (ECOG) scale was related to a preexisting disability from stroke.

‡ P<0.05.

§ The following sites were calculated as separate sites of adrenocortical carcinoma: adrenal gland (including local recurrence), liver, lung, bone, peritoneum, retroperitoneum, pleura, mediastinum, central nervous system, soft tissue, spleen, and ovary.

groups with the use of the Wilcoxon–Mann–Whitney test. (Further details are provided in Text 2 in the Supplementary Appendix.)

## RESULTS

## PATIENTS

From June 2004 through October 2009, a total of 304 patients were enrolled in the study. The database was closed for final analysis on December 10, 2010. Demographic characteristics of the patients and baseline clinical characteristics that are considered to be clinically relevant<sup>21</sup> were well balanced between the two study groups (Table 1).

## ADMINISTERED TREATMENTS

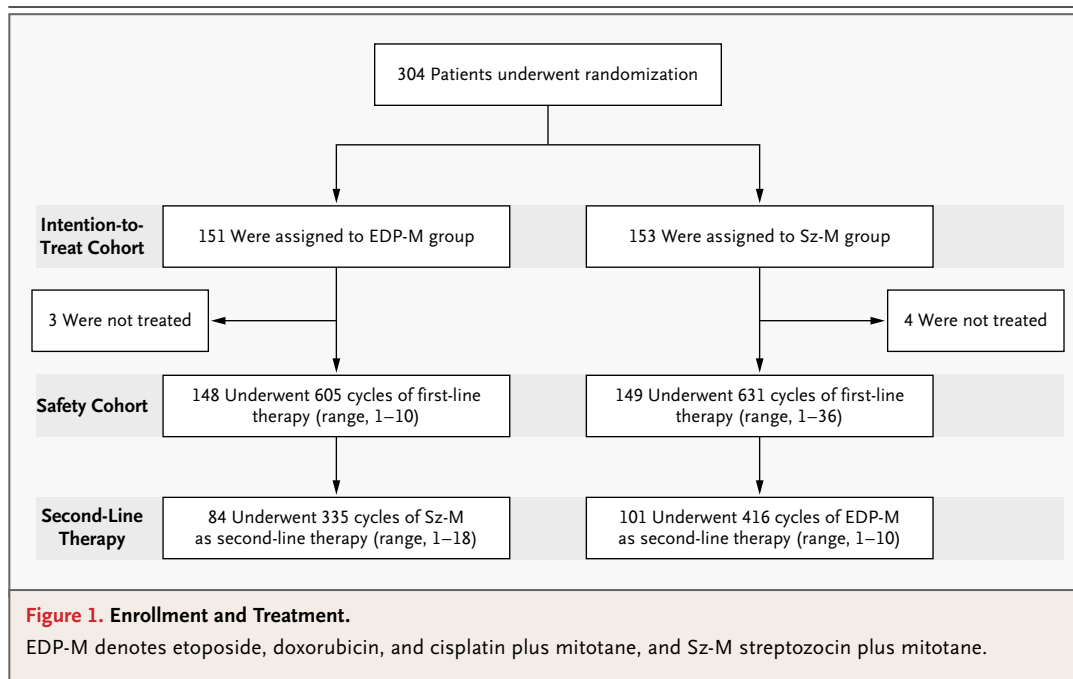
At least one cycle of chemotherapy was administered in 148 patients in the EDP–mitotane group and in 149 patients in the streptozocin–mitotane group (safety cohort) (Fig. 1). In total, 605 cycles of EDP (scheduled every 28 days) and 631 cycles of streptozocin (scheduled every 21 days) were given as first-line therapy (Table S2 in the Supplementary Appendix). The alternative regimen was administered as second-line treatment in 185 patients (EDP–mitotane in 101 patients and streptozocin–mitotane in 84 patients). However, 119 patients did not receive the second-line therapy for a variety of reasons (e.g., rapid tumor progression, toxic events that precluded further treatment, and successful first-line therapy).

## EFFICACY

*Treatment Response and Progression-free Survival*

An objective tumor response occurred in 35 of 151 patients in the EDP–mitotane group, as compared with 14 of 153 patients in the streptozocin–mitotane group (23.2% vs. 9.2%, P<0.001). Three patients had a complete response, and 6 patients were rendered disease-free by surgery after a partial response to the study treatment (Table 2).

Tumor progression occurred in 280 of 304 patients (92.1%). The median duration of progression-free survival was 5.0 months (95% confidence interval [CI], 3.5 to 6.9) in the EDP–mitotane group, as compared with 2.1 months (95% CI, 2.04 to 2.33) in the streptozocin–mitotane group (hazard ratio, 0.55; 95% CI, 0.43 to 0.69; P<0.001) (Fig. 2A). At 12 months, 26.1% of patients (95% CI, 19.0 to 33.1) who received first-line therapy with EDP plus mitotane were alive without disease progression, as compared with 7.2% (95% CI, 3.1 to 11.3) who received first-line therapy with streptozocin plus mitotane.



### Overall Survival

At final analysis, 232 patients (76.3%) had died, with 211 deaths caused by progressive disease (90.9%); 18 deaths were from causes other than cancer (infection in 6 patients, organ failure in 5, pulmonary embolism in 3, cardiovascular events in 3, and hemorrhage in 1), and 3 deaths were from unknown causes. Three deaths were classified as probably related to the EDP-mitotane regimen (infection in 2 patients and a cardiovascular event in 1) and 1 as possibly related to this regimen (a death of unknown cause 3 weeks after the administration of EDP plus mitotane). In addition, 1 patient died from liver failure 11 days after the start of treatment with streptozocin; this death was classified as most likely to be related to both the study treatment and progressive disease.

Among patients receiving first-line therapy, there were 108 deaths in the EDP-mitotane group and 124 in the streptozocin-mitotane group; the median duration of survival was 14.8 months (95% CI, 11.3 to 17.1) and 12.0 months (95% CI, 10.3 to 13.6), respectively (Fig. 2B). Thus, EDP plus mitotane as first-line treatment reduced the risk of death by 21%, as compared with streptozocin plus mitotane (hazard ratio, 0.79; 95% CI, 0.61 to 1.02;  $P=0.07$ ) in the intention-to-treat analysis. (The results of additional per-protocol analyses are provided in Text 3 in the Supplementary Appendix.)

### Subgroup Analyses

Hazard ratios for disease recurrence and death according to prespecified baseline factors are provided in Figure S1 in the Supplementary Appendix. These analyses show that the EDP-mitotane regimen had similar efficacy in most subgroups. A total of 54 patients had a blood mitotane level of 14 mg per liter or higher at baseline, and there was a trend toward increased overall survival among these patients as compared with the 212 patients who had a blood mitotane level of less than 14 mg per liter (hazard ratio for death, 0.76; 95% CI, 0.54 to 1.08;  $P=0.13$ ).

### SECOND-LINE THERAPY

The efficacy of both regimens as second-line therapy was similar to their efficacy as first-line therapy, with a median progression-free survival of 5.6 months (95% CI, 3.6 to 7.4) among the 101 patients receiving second-line EDP plus mitotane and 2.2 months (95% CI, 2.0 to 2.6) among the 84 patients receiving second-line streptozocin plus mitotane. The median duration of survival from the start of second-line therapy was 10.3 months (95% CI, 8.8 to 12.6) and 7.4 months (95% CI, 6.3 to 9.2) in the two groups, respectively. (Additional subgroup analyses are provided in Text 3 in the Supplementary Appendix.)



**Table 2. Best Overall Response in the Intention-to-Treat Population.\***

Variable	EDP-M (N=151)	Sz-M (N=153)	P Value
Type of response — no. (%)			
Complete response	2 (1.3)	1 (0.7)	
Disease-free by time of surgery†	4 (2.6)	2 (1.3)	
Partial response	29 (19.2)	11 (7.2)	
Stable disease‡	53 (35.1)	34 (22.2)	
Progressive disease	43 (28.5)	88 (57.5)	
Did not receive treatment	3 (2.0)	4 (2.6)	
Could not be evaluated for response	17 (11.3)	13 (8.5)	
Objective response§			
No. of patients	35	14	
% (95% CI)	23.2 (16.7–30.7)	9.2 (5.1–14.9)	<0.001
Disease control¶			
No. of patients	88	48	
% (95% CI)	58.3 (50.0–66.2)	31.4 (24.1–39.4)	<0.001

\* Responses were rated according to the Response Evaluation Criteria in Solid Tumors (RECIST).

† Surgery was performed after a partial response to study treatment. These patients were not included in the “partial response” category.

‡ Stable disease was defined as no disease progression for at least 8 weeks and no objective response to treatment. Confirmatory scans were not required for this determination, according to the study protocol.

§ Objective response was defined as a complete or partial response.

¶ Disease control was defined as a complete response, a partial response, or stable disease.

#### QUALITY OF LIFE AND SAFETY

The rate of compliance with the quality-of-life questionnaire was 67.1% at baseline (204 of all 304 patients) and 46.1% at the time of the first evaluation (129 of the 280 patients who were still alive). The median score was the same in the EDP-mitotane group and the streptozocin-mitotane group, both at baseline (58) and at the first evaluation (50), with no significant difference between the two evaluations (Table S3 in the Supplementary Appendix).

During the first-line therapy, 47 patients in the EDP-mitotane group had 86 serious adverse events, as compared with 37 patients with 62 serious adverse events in the streptozocin-mitotane group ( $P=0.16$ ) (Table 3). The numbers of serious adverse events per month were similar in the two study groups (0.092 per month in the EDP-mitotane group and 0.099 per month in the streptozocin-mitotane group,  $P=0.64$ ). The findings were similar for the first 8 weeks of treatment, with 45 serious adverse events in 25 patients in the EDP-mitotane group and 33 such events in 26

patients in the streptozocin-mitotane group ( $P=0.96$ ). Similarly, the rate of nonserious adverse events did not differ significantly between the two study groups (0.54 per month in the EDP-mitotane group and 0.49 per month in the streptozocin-mitotane group,  $P=0.17$ ).

#### DISCUSSION

In our study, EDP plus mitotane administered as first-line therapy in patients with advanced adrenocortical carcinoma resulted in a higher rate of objective tumor response than did streptozocin plus mitotane (23.2% vs. 9.2%), with a significant increase in progression-free survival (5.3 months vs. 2.0 months) and a significantly higher percentage of patients without progression at 12 months (26.1% vs. 7.2%). These findings suggest that EDP plus mitotane, as compared with streptozocin plus mitotane, had superior antitumor efficacy in the patients. However, despite these positive results, the overall survival rates in our study remained dismal. First-line therapy with EDP plus mitotane did not translate into a significant improvement in overall survival, as compared with streptozocin plus mitotane (14.8 months vs. 12.0 months,  $P=0.07$ ).

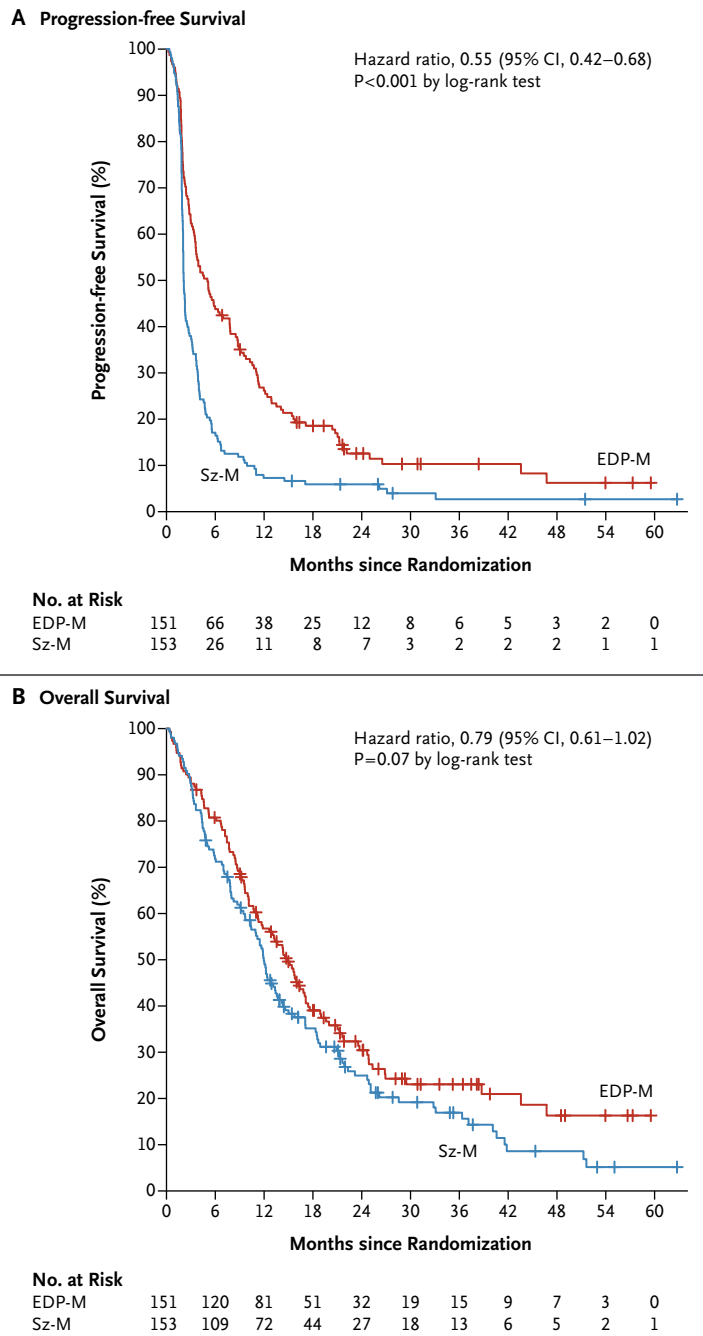
Several explanations might account for this finding, including a poorer prognosis than anticipated<sup>16,17</sup> and a smaller effect size than initially hypothesized. To provide patients with the best salvage therapy and to control for second-line treatments, the alternative regimen was included in the protocol for all patients with disease progression. Thus, two parallel phase 2 trials for second-line treatment were embedded in the study design. Although a direct statistical comparison of the results of the second-line regimens is potentially biased, the rate of progression-free survival with the two second-line regimens (5.6 months with EDP plus mitotane vs. 2.0 months with streptozocin plus mitotane) replicated the rates observed with first-line therapy, again pointing to a greater efficacy for EDP plus mitotane. Thus, the EDP-mitotane regimen was superior as first-line therapy and was also effective as second-line therapy. The efficacy of EDP plus mitotane as second-line therapy probably attenuated its advantage as first-line therapy and affected the overall survival analysis. Furthermore, it has recently been reported that mitotane is a potent inducer of CYP3A4 activity,<sup>22,23</sup> which may have reduced the blood levels of doxorubicin and eto-

poside, both of which are metabolized by CYP3A4. In theory, this could have attenuated the efficacy of the EDP-mitotane regimen. However, since no monitoring of the blood levels of these drugs was performed, we cannot evaluate these hypotheses.

The quality-of-life scores were the same in the two study groups. However, compliance in answering the questionnaires was only about 50%, thus limiting the interpretation of the data. As expected, the profile of serious adverse events differed between the two groups, but there was no significant between-group difference in the rate of such events.

Both treatment regimens contained the adrenolytic compound mitotane, which is still the only drug licensed for the treatment of adrenocortical carcinoma. Several small studies have suggested that the antineoplastic activity of mitotane monotherapy is increased at blood drug levels of 14 mg per liter or higher.<sup>8,9,24</sup> In our study, only 54 patients had such blood mitotane levels at the time of enrollment, with a similar distribution in the two study groups. Thus, any antitumor activity of mitotane is unlikely to have been a major confounder of the observed first-line efficacy of the EDP-mitotane regimen. There was a trend toward increased overall survival among these 54 patients as compared with the 212 patients with a mitotane level of less than 14 mg per liter (hazard ratio for death, 0.76), although the small numbers require caution in the interpretation of this observation.

One of the strengths of our trial was the size of the study cohort, which was larger than the combined number of participants enrolled in all published phase 2 trials of treatment for adrenocortical carcinoma. An international network of closely collaborating investigators was the key to achieving this enrollment of patients within only 5.4 years, which is equivalent to a recruitment rate of 56 patients per year, as compared with a maximum of 7 patients per year in previous studies.<sup>17,25-28</sup> This successful enrollment shows that an investigator-initiated, randomized phase 3 trial of treatment in patients with a rare tumor is feasible, despite the lack of pharmaceutical interest in sponsoring such a trial. Further strengths of the trial include its prospective, randomized design; the intention-to-treat analysis; the high percentage of patients who were evaluated for the predefined end points; and the small number of censored observations. In addition, the trial was conducted in 12 countries on three continents, and the inclusion criteria were



**Figure 2. Progression-free and Overall Survival during First-Line Therapy.**

Panel A shows Kaplan–Meier estimates for progression-free survival during first-line therapy. The median duration of progression-free survival was 5.0 months in the EDP-M group and 2.1 month in the Sz-M group. Panel B shows Kaplan–Meier estimates for overall survival, with a median of 14.8 months in the EDP-M group and 12.0 months in the Sz-M group.

broad, with few exclusion criteria. Thus, the study population can be considered to be representative of the overall population of patients with advanced

**Table 3. Serious Adverse Events during First-Line Therapy.**

Event	EDP-M (N=148) <i>no. of patients (%)</i>	Sz-M (N=149) <i>no. of patients (%)</i>
Any serious adverse event	86 (58.1)	62 (41.6)
Adrenal insufficiency	5 (3.4)	1 (0.7)
Bone marrow toxicity	17 (11.5)	3 (2.0)
Cardiovascular or thromboembolic event	10 (6.8)	0
Fatigue or general health deterioration	8 (5.4)	7 (4.7)
Gastrointestinal disorder	6 (4.1)	12 (8.1)
Impaired liver function	0	7 (4.7)
Impaired renal function	1 (0.7)	6 (4.0)
Infection	10 (6.8)	4 (2.7)
Neurologic toxicity	5 (3.4)	4 (2.7)
Respiratory disorder	9 (6.1)	5 (3.4)
Other	15 (10.1)	13 (8.7)

adrenocortical carcinoma, and the findings should be generalizable to this larger population.

Although new targeted therapies have been successfully introduced for various cancers, the initial results of small studies evaluating such therapies in patients with adrenocortical carcinoma have been disappointing.<sup>29-34</sup> The tumor response in our study compares favorably with

the results obtained with these novel therapies. Nonetheless, the poor overall survival rates in our study confirm the poor prognosis for patients with advanced adrenocortical carcinoma and the need for improved treatment options.

In summary, although a significant improvement in overall survival was not achieved with EDP plus mitotane as first-line therapy, this regimen had higher antitumor efficacy as both first- and second-line therapy than did streptozocin plus mitotane, with a similar rate of serious adverse events.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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#### APPENDIX

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