First International Randomized trial in locally advanced and Metastatic Adrenocortical Carcinoma Treatment (FIRM-ACT)

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Protocol synopsis

Sponsor	Collaborative group for Adrenocortical Carcinoma Treatment (CO-ACT)
Objectives	To compare the efficacy of etoposide, doxorubicin and cisplatin plus mitotane (EDP/M) as first line treatment versus streptozotocin plus mitotane (Sz/M) as first line treatment
Study design	Randomized, prospective, controlled, open -label multicenter, parallel-group study
Sample size	300 patients (150 per regimen)
Inclusion criteria	• Histologically confirmed diagnosis of adrenocortical carcinoma • Locally advanced or metastatic disease not amenable to radical surgery resection (Stage III-IV) • Radiologically monitorable disease • ECOG performance status 0-2 • Life expectancy > 3 months • Age ≥18 years • Adequate bone marrow reserve (neutrophils ≥1500/mm^3 and platelets ≥100.000/mm^3) • Effective contraception in pre-menopausal female and male patients • Patient's written informed consent • Ability to comply with the protocol procedures (including availability for follow-up visits) • Previous palliative surgery, radiotherapy or radiofrequency ablation is acceptable as long as radiologically monitorable disease is verifiably afterwards.

Exclusion criteria	• History of prior malignancy, except for cured non-melanoma skin cancer, curatively *in situ* cervical carcinoma, or other cancers treated with no evidence of disease for at least five years. • Previous cytotoxic chemotherapy for adrenocortical carcinoma • Renal insufficiency (serum creatinine ≥2 mg/dl or creatinine clearance ≤ 50 ml/min) • Hepatic insufficiency (serum bilirubin ≥2 x the institutional upper limit of normal range and/or serum transaminases ≥ 3 x the institutional upper limit of normal range; exception: in patients on mitotane transaminase levels up to 5 x the institutional upper limit of normal range are acceptable) • Pregnancy or breast feeding • Known hypersensitivity to any drug included in the treatment protocol • Presence of active infection • Any other severe clinical condition that in the judgment of the local investigator would place the patient at undue risk or interfere with the study completion • Decompensated heart failure (ejection fraction <50%), myocardial infarction or revascularization procedure during the last 6 months, unstable angina pectoris, and uncontrolled cardiac arrhythmia • Current treatment with other experimental drugs and/or previous participation in clinical trials with other experimental agents for adrenocortical carcinoma • Prisoners
Endpoints	Primary endpoint: to compare overall survival Secondary endpoints: • To compare quality of life • To compare time to progression, best overall response rate, duration of response, and number of disease-free patients • To assess the impact of mitotane blood levels between 14-20 mg/l in both regimens on survival and response • To assess the effects of both schemes as a second line treatment in case of failure of the other regimen (measured by best overall response)
Treatment schedule	Patients will be randomly assigned to receive: I) Etoposide, Doxorubicin and Cisplatin (EDP) plus Mitotane (EDP/M) on day 1 40mg/m^2 D, day 2 100mg/m^2 E, day 3+4 100mg/m^2 E + 40mg/m^2 P; every 28 days plus oral mitotane aiming at a blood level between 14-20mg/l II) Streptozotocin plus Mitotane (Sz/M) Induction day 1-5 1g Sz/d. Afterwards 2g/d Sz every 21 days plus oral mitotane aiming at a blood level between 14-20mg/l Evaluation of response is scheduled every 8 weeks in the first 6 months after beginning first line and second line treatment, respectively, and afterwards every 12 weeks. In case of documented disease progression or unacceptable toxicity, subjects will be switched to the alternative regimen.
Statistical analysis	The main statistical analysis of the primary endpoint will be based on the intention-to-treat (ITT) population. For each treatment group the overall survival distribution and the median survival time will be estimated using the Kaplan-Meier method. The two-sided logrank test at a 0.05 significance level will be used to test the survival time null hypothesis assuming proportional hazards. For the hazard ratio a point estimate and a 95% confidence interval will be provided. One interim analysis without alpha spending and two interim analyses with alpha spending are planned. The final analysis will be conducted after 200 observed events (deaths).
Trial duration	7 years (Recruitment period: 60 months. Follow-up period: 18 months. Data base validation prior to data base lock and final analysis: 6 months)