

# Efficacy of adjuvant mitotane treatment in prolonging recurrence -free survival in -patients with adrenocortical carcinoma at low-intermediate risk of recurrence

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Primary objectiveTo compare the efficacy of adjuvant mitotane treatment vs observational follow-up only in prolonging recurrence free survival (RFS) in patients with ACC after complete resection and low-intermediate risk for disease recurrence....

<b>Ethical review</b>	Approved WMO
<b>Status</b>	Recruitment stopped
<b>Health condition type</b>	Adrenal gland disorders
<b>Study type</b>	Interventional

## Summary

### ID

NL-OMON36658

### Source

ToetsingOnline

### Brief title

ADIUVO

### Condition

- Adrenal gland disorders

### Synonym

adrenocortical carcinoma, carcinoma of the adrenal cortex

### Research involving

Human

### Sponsors and support

**Primary sponsor:** Azienda Ospedaliera S. Luigi Gonzaga

**Source(s) of monetary or material Support:** HRA Pharma, medicatie en analysering van circulerende mitotane spiegels worden door bedrijf gesponsord; de rest uit eigen middelen onderzoekers

## Intervention

**Keyword:** adrenocortical carcinoma, mitotane

## Outcome measures

### Primary outcome

Recurrence free survival, defined as the time between the date of randomization until documentation of any of the following failures (whichever occurs first):

- local or distant recurrence of ACC
- death from any cause or completion of follow-up

### Secondary outcome

- Overall survival, defined as the time between the date of randomization and the date of death from any cause
- Time to recurrence, defined as the time between the date of randomization until documentation of local or distant recurrence of ACC, or death from ACC
- disease free survival, defined as the time between the date of randomization until documentation of any relevant cancer disease, or death of any cause (whichever occurs first)
- Quality of life measured by EORTC-QLQ-C30

## Study description

### Background summary

Adrenocortical carcinoma is a very rare disease with a high risk of relapse after radical surgery. The efficacy of adjuvant mitotane treatment is suggested

by a retrospective multicenter international study showing that postoperative mitotane treatment was associated with a significant reduction of the risk of relapse and death. However, these promising results need confirmation in a randomized prospective study. Caution should be adopted particularly in patients with low risk of disease relapse, in whom the benefit of therapy should be weighted against the side effects. Even if an adjuvant treatment seems justified in patients at high risk of relapse, a randomized prospective study is needed to assess whether such a treatment is efficacious in patients at low-intermediate risk.

## **Study objective**

### Primary objective

To compare the efficacy of adjuvant mitotane treatment vs observational follow-up only in prolonging recurrence free survival (RFS) in patients with ACC after complete resection and low-intermediate risk for disease recurrence.

### Secondary objectives

- \* Comparison of Overall Survival (OS)
- \* Comparison of time to recurrence (TTR)
- \* Comparison of disease free survival (DFS)
- \* Quality of life assessment
- \* Assessment of toxicity
- \* Assessment of the impact of mitotane plasma levels and time needed to reach the therapeutic interval on the efficacy of treatment
- \* Assessment of the efficacy of the mitotane administration in predefined subgroups of patients stratified according to:
  - type of hormone secretion,
  - stage of disease,
  - histopathologic characteristics .

## **Study design**

Prospective ,randomized , controlled, open-label, multi-center phase III trial

## **Intervention**

Patients will be randomly assigned to receive mitotane treatment or observational follow up only. The daily dose of the drug should be increased if plasma levels of the mitotane are below 14 mg/l. Reduction of mitotane dosage should be considered if plasma levels are over 20 mg/l or toxicity does occur. Mitotane will be administered until progression or unacceptable toxicity for a minimum of 2 years.

## **Study burden and risks**

The burden and risks associated with participation are constituted by the possible side effects of mitotane:

- adrenal insufficiency (steroidhormone suppletion starts with mitotane by default)
- gastro-intestinal disturbances
- liver enzyme alterations
- neurological toxicity
- hormone alterations

## Contacts

### Public

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### Scientific

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## Trial sites

### Listed location countries

Netherlands

## Eligibility criteria

### Age

Adults (18-64 years)

Elderly (65 years and older)

### Inclusion criteria

Histologically confirmed diagnosis of ACC.

Low-intermediate risk of relapse defined as: stage I-III ACC(according to the ENS@T

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classification 2008).

Microscopically complete resection, defined as no evidence of microscopic residual disease based on surgical reports, histopathology and post-operative imaging.

Ki67 index  $\leq$  or equal 10 %.

Post-operative imaging demonstrating no evidence of disease within 4 weeks before randomization.

ECOG performance status 0-2.

Age equal to or older than 18 years

Adequate bone marrow reserve (neutrophils equal or higher than  $1.0 \times 10^9/L$  and/or platelets equal or higher than  $80.0 \times 10^9/L$ )

Ability to comply with the protocol procedures

Written informed consent

## Exclusion criteria

Time between primary surgery and randomization  $> 3$  months.

Repeated surgery for recurrence of disease.

Renal insufficiency (creatinine clearance  $< 40$  ml/min) or liver insufficiency (serum bilirubin  $> 2$  times the upper normal range and/ or serum transaminase (AST,ALT)  $> 3$  times the upper normal range).

History of recent or active prior malignancy, except for cured non melanoma skin cancer, cured insitu cervical carcinoma, or other treated malignancies where there has been no evidence of disease for at least three years.

Previous or current treatment with mitotane or other antineoplastic drugs for ACC.

Previous radiotherapy for ACC.

## Study design

### Design

Study phase: 3

Study type: Interventional

Intervention model: Parallel

Allocation: Randomized controlled trial

Masking: Open (masking not used)

**Primary purpose:** Treatment

### Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	05-10-2011
Enrollment:	16
Type:	Actual

## Medical products/devices used

Product type:	Medicine
Brand name:	Lysodren
Generic name:	Mitotane
Registration:	Yes - NL intended use

## Ethics review

Approved WMO	
Date:	01-11-2010
Application type:	First submission
Review commission:	METC Maxima Medisch Centrum (Veldhoven)
Approved WMO	
Date:	18-02-2011
Application type:	Amendment
Review commission:	METC Maxima Medisch Centrum (Veldhoven)

## Study registrations

### Followed up by the following (possibly more current) registration

No registrations found.

### Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

### Register

EudraCT

ClinicalTrials.gov

CCMO

### ID

EUCTR2007-007262-38-NL

NCT00777244

NL29842.015.10