Clinical Study Report

"Sunitinib in Refractory Adrenocortical-Carcinoma patients progressing after cytotoxic chemotherapy (SIRAC)"

Name or abbreviated title:	SIRAC
Clinical investigation plan ID:	**SIRAC-1**
Investigational product:	**Sunitinib malate capsules of 12.5, 25 and 50 mg**
Sponsor /contact details:	Universitätsklinikum Würzburg Josef-Schneider-Str. 2 97080 Würzburg
Coordinating investigator:	Prof. Dr. M. Fassnacht
Statistician:	Prof. Dr. H.-H. Müller
Start of trial:	**16.07.2007**
End of trial:	**Lock of the database: 01. Aug 2011** **Final analyses: 10. Feb 2012**
Number of patients included:	**39**
Author(s) of report:	**Prof. Dr. M. Fassnacht** **Prof. Dr. M. Quinkler** **Prof. Dr. M. Kroiß**
Version / date:	**Vs. 2.0 / 30.12.2020**

Sponsor:

University Hospital Würzburg, Josef-Schneider-Str. 2, 97080 Würzburg

Name of Finished Product:

Sutent (12.5, 25 and 50 mg)

Name of Active Substance:

Sunitinib (SU011248)

Title of Study:

"Sunitinib in Refractory Adrenocortical-Carcinoma patients progressing after cytotoxic chemotherapy (SIRAC)"

Sponsor Protocol Code: SIRAC-1 (no Amendments)

Investigators:

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Publication (reference):

J Clin Endocrinol Metab . 2012 Oct;97(10):3495-503. doi: 10.1210/jc.2012-1419. Epub 2012 Jul 26

Phase of development:

Phase II

Objective of the investigation:

To determine the effects of Sunitinib in patients with advanced ACC progressing after cytotoxic chemotherapy, primary to demonstrate a response rate of more than 5% and to estimate the response rate with confidence

Clinical endpoints: Progression-free survival of ≥ 12 weeks defined as a response (primary); Assessment of Objective Response Rates (ORR) and duration of response (DR), Assessment of progression-free survival, Assessment of overall survival, Assessment of the relationship between specific "biomarker" and cancer and treatment-related outcomes, Assessment of quality of life by EORTC QLQ-C30, Assessment of toxicity

Methodology:

Prospective, non-randomized, open-label, single arm, multicenter study

Number of patients (planned / evaluated): 36 / 39

Diagnosis and main criteria for inclusion:

Adrenocortical carcinoma progressing after cytotoxic chemotherapy

- Histologically confirmed diagnosis of ACC
- Locally advanced or metastatic disease not amenable to radical surgery resection
- Radiologically monitorable disease
- Progressing disease after mitotane treatment and one to three cytotoxic chemotherapy regimes including a platin-based protocol
- ECOG performance status 0-2
- Life expectancy ≥ 3 months
- Age ≥ 18 years
- Adequate bone marrow reserve (neutrophils ≥ 1500/mm³ and platelets ≥100.000/mm³) and haemoglobin ≥ 9 g/dl
- Negative pregnancy test and effective contraception in pre-menopausal female and male patients
- Patient´s written informed consent

Test product:

Sunitinib (SU011248)

Dose and mode of administration: 50 mg/d orally for 4 weeks followed by a 2-week-off-periode (= 1 cycle) – down titration to 37.5 and 25 mg possible due to tolerability issues.

Investigational Product: provided by Pfizer as hard gelatin capsules containing

- 12.5 mg – Batch Numbers 06-042994 and 07-050205
- 25 mg – Batch Numbers 05-033391 and 07-050207
- 50 mg – Batch Numbers 06-047124 and 07-050208

Duration of treatment:

Until documented disease progression or unacceptable toxicity.

Reference therapy:

Not applicable

Criteria for evaluation:

Efficacy: Evaluation of response was performed according to RECIST criteria scheduled every 84±5 days (12 weeks) up to the onset of progression. The primary endpoint was progression-free survival (PFS) after 12 weeks - defined as response.

Safety: During the course of the study, changes in physical findings as well as clinical signs and symptoms and laboratory findings were documented. All AEs and SAEs were graded according to the NCI-CTG Criteria (version 3.0) and evaluated with regard to relation to the investigational product.

Statistical methods:

To minimize the number of patients treated, the optimal two-stage accrual design by Simon has been adopted. The null-hypothesis of a response rate ≤5% was tested, and the time to progression and to death calculated with 95% (and with 90%) confidence interval (CI) was reported after stage-wise ordering according to Clopper and Pearson.

Summary of results:

Efficacy Results:

The first patient was included in the study on July 17, 2007, the last patient enrolled on September 18, 2009. The last patient stopped the study drug on November 20, 2009. Data collection was closed on August 1, 2011 when three patients were still alive. The analyses were finalized February 10, 2012.

Remaining study medication was sent back to Pfizer Pharma and destroyed by 30th Aug 2010.

The **study population** is characterized in detail in **Table 1**.

Four patients had to be excluded from the per protocol analysis: In one patient (PID16), the review of tumor specimens by the reference pathologist revealed misdiagnosis of a malignant pheochromocytoma as ACC. This patient had stable disease at 12 weeks, progressed after 164 days and died 63 weeks after starting sunitinib. One patient (PID 29) experienced a serious adverse event (dyspnea due to heart failure) unrelated to the study treatment and withdrew further study treatment 42 days after enrollment. One patient (PID 21) had a myocardial infarction considered to be possibly treatment related which led to discontinuation of the study drug after 9 1/2 weeks of treatment. Imaging outside the study suggested progressive disease and the patient died 2 months later. One patient (PID 5) was excluded from the study due to incompliance with the study procedures after eight weeks. However, the appearance of a new metastatic skin lesion suggested progressive disease and the patient died after 43 weeks. Thus, 35 patients were analyzed for response on a per protocol basis.

Characteristic	No. of patients
Sex	
male	17
female	22
Age, y	
median	51.4
range	22-72
ECOG performance status	
0	16
1	20
2	3
Mitotane therapy	
patients (number)	24
Mitotane plasma level	
median	11.6
range	<1.0-33.7
Steroid hormone secretion	
Glucocorticoid excess	
clinically apparent	7
biochemical only	2
Androgen excess	
clinically apparent	10
biochemical only	7
Estrogen excess	
clinically apparent	3
biochemical only	4
Mineralocorticoid excess	
Biochemical only	1
Weiss score (n=35)	
median	6
range	4-9
Ki67 index (n=35)	
median	20%
range	2-50%

Characteristic	No. of patients
Prior cytotoxic chemotherapies	
EDP	
patients (number)	38
median (no. of cycles)	5
range (no. of cycles)	1-10
Streptozotocin	
patients (number)	35
median (no. of cycles)	4
range (no. of cycles)	1-18
other	
patient (number)	6
median (no. of cycles)	5
range (no. of cycles)	1-13
Baseline target lesions (RECIST)	
median	207
range	60-351
Baseline target lesions (number)	
median	7
range	2-10
Sites of target lesions (no. of patients)	
adrenal	15
liver	27
local lymph nodes	5
distant lymph nodes	12
lung	26
peritoneum	10
kidney	4
skin and soft tissue	5
spleen	2
bone	1*
Baseline non-target lesions (no. of patients)	
lung	21
bone	5
liver	3
kidney	1
peritoneum	2
spleen	2
other	2

Table 1: Patient characteristics at study inclusion of the entire study cohort (n=39)

*PID15, the patient with malignant pheochromocytoma

The **primary endpoint** of the study was 12-week progression-free survival in patients treated per protocol. Of these 35 patients, six patients died of progressive disease prior to first radiologic evaluation at 12 weeks. Of the remaining 29 patients, five patients experienced stable disease, and 23 patients had progressive disease (Figure 1) at first evaluation. No partial or complete tumor response according to RECIST criteria was observed.

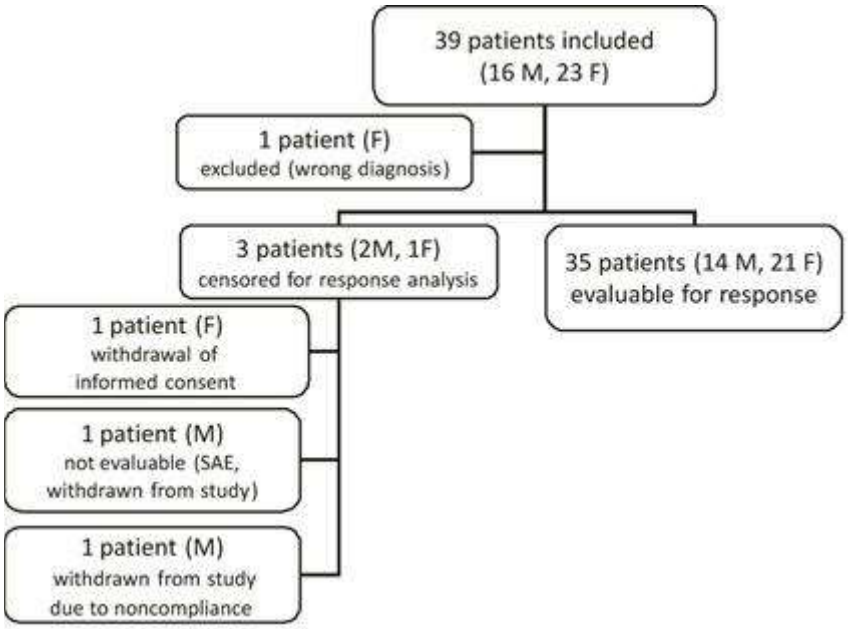
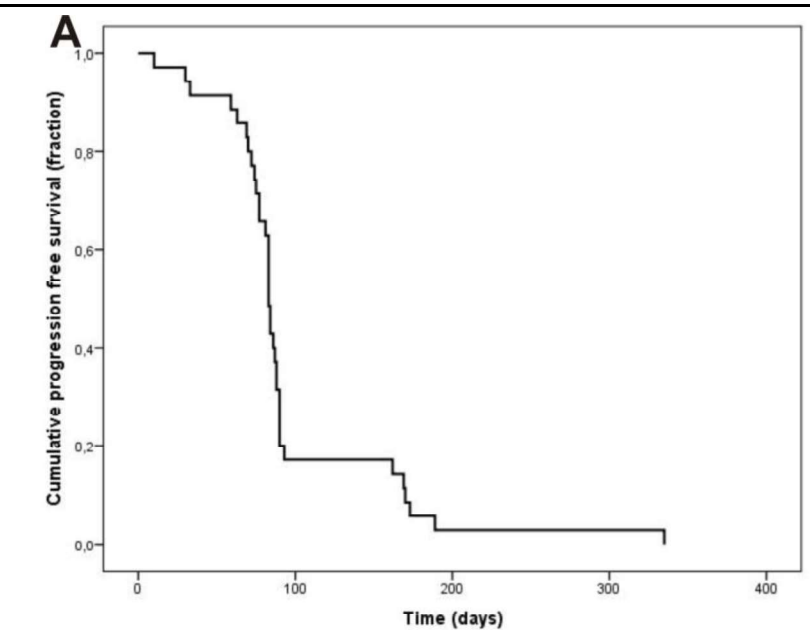


Figure 1: CONSORT diagram

Of the five patients with stable disease at first evaluation, three patients showed disease progression at the second evaluation. One patient (PID 7) had progressive disease after 11.2 months of treatment and in PID 12 sunitinib was withdrawn after diagnosis of progressive disease was made at second evaluation. However, central review later indicated stable disease leading to censoring of this patient at this time point. The patient finally progressed after 5.7 months and deceased from ACC after 35.5 months. Thus, the null-hypothesis (5% response rate) could be rejected (p=0.0247 one-sided) and the estimated response rate was 14.3% in a naïve estimate. The median unbiased estimate was 15.4% (90% CI 6.1%-30.0%, 95% CI: 5.01%-33.4%). In addition, we performed an intention-to-treat analysis with all 39 patients assessing one patient (PID 29) conservatively as a non-responder. This sensitivity analysis leads to p=0.0107 (one-sided) and an estimated response rate of 15.4 % naïve and of 16.3% (90% CI 7.2%-30.2%, 95% CI: 6.1%-33.5%) unbiased.

In the cohort of the 35 per protocol evaluated patients, median PFS was 84 days (95% CI, 80-88 days, Figure 2A), exactly the time of the first evaluation. Median overall survival was 5.4 months (95% CI, 3.2-7.6 months, Figure 2B). At the time of closing of data collection, one patient was still alive with a maximum follow-up of 2.5 years.



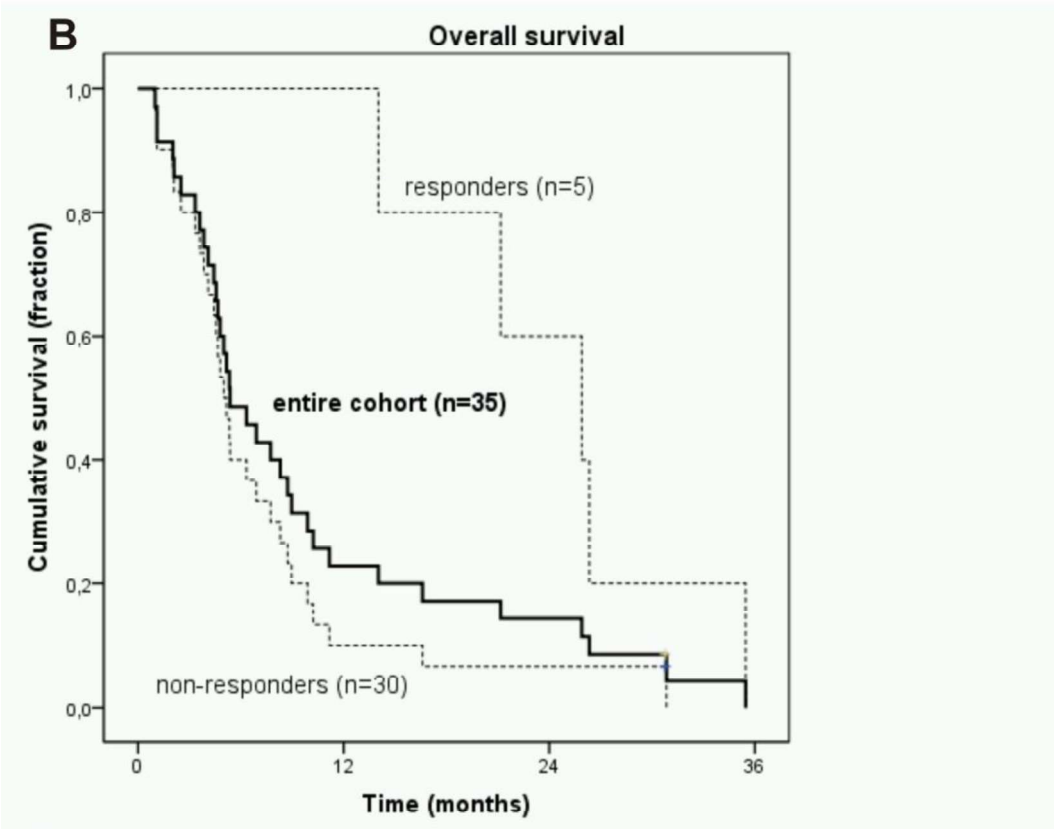


Figure 2: (A) Progression free survival and (B) overall survival (n=35)

It is noteworthy that amongst the patients who responded to the treatment at first evaluation, PFS ranged between 5.6 and 11.2 months and overall survival between 14.0 and 35.5 months (Figure 2B).

Safety Results:

A total of 158 **adverse events** were recorded with a median number of adverse events per patient of 4.0 (range 0-10). The majority of adverse events were CTC grade 1 or 2 (66%), with the most common non-hematologic adverse events being polyneuropathy (n=11 in 10 patients), pain (n=19 in 12 patients), infections (n=15 in 10 patients), diarrhea (n=9 in 9

patients). Surprisingly, treatment related adverse events typically observed with multi-tyrosine kinase inhibitors, such as fatigue (n=3), hand-foot reactions, rash or discolored nails (n=9), and mucositis (n=4) were generally mild or absent (hypertension). Hematologic laboratory abnormalities were also only mild or moderate. There was one grade 4 hypoglycemia, which was considered to be possibly related to sunitinib, but was probably related to high glucose utilization by a large tumor mass.

In total, of the 158 adverse events, only 42 were considered to be related to sunitinib treatment and only 13 of these were grade 3 and three grade 4 events (Table 2).

Category	Adverse Event	CTC1+2	CTC3	CTC4
Gastrointestinal	Diarrhea	5	2	0
	Hemorrhoids	1	0	0
Liver	elevated liver enzymes	0	2	0
	jaundice	1	0	0
	liver failure	0	1	0
Dermatology	Mucositis/stomatitis	4	0	0
	Skin rash	2	0	0
	Hand-foot skin reaction	1	0	0
	Dry skin	1	0	0
	Discolored nails	1	0	0
Hematology	Anemia, thrombopenia, Leukopenia	2	2	0
	Thrombosis	0	1	0
Hemorrhage	1x gastrointestinal, 1x respiratory tract, 1x skin	3	0	0
Endocrinology	Hypoglycemia	0	0	1
	Adrenal insufficiency	0	1	0
Cardiac	Myocardial infarction	0	0	1
	Syncope	0	0	1
Constitutional	Fatigue	0	2	0
	Muscle weakness	1	0	0
Neurology	Dizziness/drowsiness	0	2	0
	Polyneuropathy	3	0	0
Pain	Abdominal pain	1	0	0

Table 2: Adverse events considered to be at least possibly related to the study treatment.

Forty-four serious adverse events (SAE) were recorded, but only ten were judged to be possibly related to the study drug. A comprehensive list of serious adverse events is given in Table 2.

adverse event	Date AE	CTC Grade	treatment related
liver failure	21.02.2008	5	1
tumor progression	10.09.2008	5	1
tumor progression	19.11.2008	5	1
tumor progression	19.01.2009	5	1
tumor progression	04.06.2009	5	1
tumor progression	20.11.2009	5	1
recurrent syncope	12.08.2007	4	3

sepsis	22.11.2007	4	2
renal failure	22.11.2007	4	2
hyperkalemia	12.02.2008	4	1
somnolence	15.06.2008	4	1
oesophagitis	16.06.2008	4	1
acute cauda syndrome	01.07.2008	4	2
hypoglyemia	27.08.2008	4	3
back pain due to metastasis	14.09.2008	4	1
myocardial infarction	14.10.2008	4	3
back pain due to metastasis	23.11.2008	4	1
abscess	13.12.2008	4	2
perianal fistulation	13.12.2008	4	1
hypotension	19.01.2009	4	1
surgery for bone metastasis	09.04.2009	4	1
abdominal pain	10.11.2009	4	1
surgery for soft tissue metastasis	02.11.2007	3	3
gastroenteritis	11.03.2008	3	3
urinary tract infection	11.04.2008	3	2
somnolence, vertigo, diplopia	23.05.2008	3	1
back pain due to metastasis	01.09.2008	3	1
urinary tract infection	01.09.2008	3	1
urosepsis	19.10.2008	3	1
prostration	24.10.2008	3	1
liver failure	30.10.2008	3	3
adrenal crisis	10.11.2008	3	3
dyspnea	15.01.2009	3	1
thrombosis left arm	23.02.2009	3	3
anemia	09.06.2009	3	2
diarrhea due to C. diff. Colitis	12.02.2008	2	3
rise of crp, fever	19.09.2008	2	1
constipation	19.10.2008	2	1
thrombopenia	07.11.2008	2	3
renal failure	07.11.2008	2	1
urinary tract infection	23.11.2008	2	1
gastrointestinal bleeding	03.04.2009	2	3
anemia	23.07.2009	2	2
anemia	02.11.2009	2	1

Table 3: Serious adverse events in 39 patients treated with sunitinib; treatment relatedness is encoded as: 1=unrelated to treatment; 2=unlikely to be related to treatment; 3= possibly related to treatment; 4=probably related to treatment; 5=definitely related to treatment

In an unplanned exploratory analysis, we analyzed the **impact of mitotane co-treatment** on the outcome of patients. Surprisingly, of the 5 patients with stable disease, only one patient had ongoing mitotane treatment. In contrast, among the 30 patients with progressive disease, 21 had ongoing mitotane treatment leading to an odds ratio for progressive disease of 9.33 (95% CI 0.91-95.63, p=0.052). Since mitotane had been stopped just shortly before inclusion in some patients and the plasma elimination half-life is up to 5 months (Hahner et al. Curr Opin Invest Drugs 2005) mitotane levels were re-assessed in 34/35 patients. In fact, mitotane serum concentrations >7 mg/l were present in 5/15 patients in whom mitotane treatment had been stopped prior enrollment. Overall, the median mitotane level at baseline examination was 11.6 mg/l (range <1-33.7 mg/l).

A pharmacokinetic observation study published after completion of the trial suggested that

mitotane strongly induces CYP3A4 activity and, therefore, diminishes the exposure of sunitinib (van Erp et al. Eur J Endocrinol 2011). Thus, in an unplanned exploratory analysis we examined the blood concentrations of sunitinib and its active metabolite N-desethylsunitinib (SU12662) during sunitinib treatment in available plasma samples that were not prospectively collected (n=7; Table 4). This study therefore does not have a study code. The median concentration was 29.3 ng/ml (range <5-56.6). Only in the single patient not treated with mitotane and with mitotane serum level <1 mg/l, the combined serum concentration of sunitinib and SU12662 was >50 ng/ml, which is considered to be required for therapeutic activity (Faivre et al. J Clin Oncol 2006) (see Table 4). Of note, SU12662 levels were generally higher than sunitinib levels which is in marked contrast to published data where median steady state concentration of SU12662 was 17.4 ng/ml and of sunitinib 40.6 ng/ml.

PID	day of treatment (treatment cycle)	sunitinib (ng/mL)	SU12662 (ng/ml)	Σ (sunitinib, SU12662)	SU12662/ sunitinib	mitotane treatment at baseline (Y/N)	mitotane levels at baseline (mg/l)	clinical outcome	adverse events (n)
2	29 (1)	23,2	33,4	56,6	1,7	N	<1	PD	2
14	4 (1)	6,76	22,5	29,26	1,3	N	17,3	PD	2
19	28 (1)	13,6	25,0	38,6	1,5	Y	11,6	PD	6
20	28 (1)	<2,5	<2,5	n/a	n/a	Y	20,0	PD	5
23	28 (2)	7,58	27,8	35,38	1,3	Y	14,8	PD	3
29	14 (1)	5,54	22,4	27,94	1,2	Y	6,5	PD	5
32	14 (2)	5,6	16,2	21,8	1,3	N	5,6	SD	7

Table 4: Influence of mitotane on serum levels of sunitinib and its primary metabolite SU12662 in a post hoc analysis of seven patients during sunitinib steady state

Furthermore, there was evidence for a negative correlation between mitotane and sunitinib serum concentrations, although this correlation was statistically not significant, most likely due to the small number of samples (Figure 3).

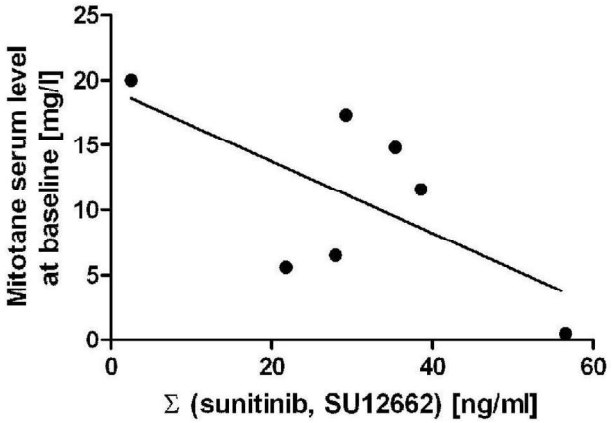


Figure 3: Correlation of serum levels of sunitinib plus its active primary metabolite vs. mitotane serum levels.

To investigate whether mitotane co-treatment affects the observed toxicity, we compared the numbers and severity of adverse events in both groups of patients. We hypothesized increased drug metabolism by mitotane to lead to lesser or less severe adverse events in mitotane treated patients. However, we found no difference.

Conclusion:

In this phase II trial, we observed moderate single-agent activity of the multi-tyrosine kinase inhibitor sunitinib in patients with refractory disease. Five of 35 evaluable patients had disease control for at least 12 weeks leading to estimates of response rate of 14.3% (naïve) and 15.4% (median unbiased), respectively. Thus, the null hypothesis (5% response rate) was rejected (p=0.0247). These results appear to compare favorably with other treatment regimens using targeted therapies tested in refractory advanced disease, as they all failed to affect disease progression. However, no direct comparison has been performed and all studies included small numbers of patients preventing final conclusions.

In the present clinical trial, five patients showed stable disease at 12 weeks. In these responding patients, median progression-free survival reached 6 months, and median overall survival 26 months.

A limitation arises from the fact that imaging prior study entry was not standardized. Therefore, we cannot provide data regarding the dynamics of tumor growth before initiation of sunitinib. Likewise, we cannot exclude that tumors responsive to sunitinib treatment might be biologically less aggressive in view of relatively low Ki67 index and Weiss score in this group.

On the other hand, the clinical efficacy of sunitinib in ACC might be under-estimated in our trial for several reasons. First, the drug interaction of mitotane with sunitinib may have greatly reduced the exposure to sunitinib. Second, extensive pretreatment of ACC with several cytotoxic regimens including cisplatin and mitotane is likely to induce drug resistance and/or selection of multi-resistant tumor clones. Our study comprised a selection of highly aggressive tumors because only patients with progressive disease after chemotherapy were eligible. Third, hitherto unknown inter-individual variability in drug target expression may account for some proportion of treatment failure.

Toxicity in our trial was relatively modest and adverse drug effects typical for tyrosine kinase inhibitors relatively rare compared to other clinical trials. The fact that we did not find differences in AE between mitotane treated and not mitotane-treated patients is most likely attributable to the overall high rate of adverse effects induced by mitotane compensating the lower sunitinib related toxicity.

Hence, we consider this clinical trial to pave the way for further evaluation of targeted therapies in the field of adrenocortical carcinoma. This trial also clearly demonstrated – a as an undesired result – the potential clinical impact of mitotane treatment on the pharmacokinetic of other drugs, in particular tyrosine kinase inhibitors by increasing their metabolism.

Overall we envisage to investigate the utility of treatment with sunitinib in a consecutive clinical trial of patients with ENSAT stage IV tumors not (yet) treated with mitotane accompanied by thorough therapeutic drug monitoring throughout the study.

Date of Report: 30th December 2020