Clinical trial results:
A randomized phase II study to explore the efficacy and feasibility of upfront rotations between sunitinib and everolimus versus sequential treatment of first line sunitinib and second line everolimus until progression in patients with metastatic clear cell renal cancer.

Summary

EudraCT number	2012-001337-13
Trial protocol	ES GR
Global end of trial date	27 December 2017

Results information

Result version number	v1 (current)
This version publication date	03 May 2018
First version publication date	03 May 2018
Summary attachment (see zip file)	Protocol synopsis (Protocol synopsis SUNRIES v 4.0.pdf) Sunrises_Clinical Study Report (SUNRISES_CSR_Ver. 1.0 - Final_12Feb2018 (002).docx)

Trial information

Trial identification

Sponsor protocol code	11CRAD001LIC34T

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01784978
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	APRO
Sponsor organisation address	Passeig del Mar, Barcelona, Spain,
Public contact	Inma Musté, APRO, 0034 93248 30 00, oncologia.apro@gmail.com
Scientific contact	Inma Musté, APRO, 0034 93248 30 00, oncologia.apro@gmail.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 December 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 April 2017
Global end of trial reached?	Yes
Global end of trial date	27 December 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Progression-free survival (PFS) rate at 1 year

Protection of trial subjects:

The protocol and the patient information sheet and informed consent form (ICF) were reviewed and approved by the institutional review board (IRB)/ Independent Ethics Committee (IEC) involved and by the reference IRB/IEC, which provided in writing to the sponsor its approval/favorable opinion regarding the study development.
According to IEC regulations all patients gave their consent by signing the approved ICF before any procedures specified in the protocol were performed. The sponsor submitted the required reports of the study progress to the IRB/IEC and to communicate the eventual serious adverse events (SAE), AES that were considered life-threatening or the deaths. The sponsor informed the IEC of the termination of the study.
This study was conducted in accordance with the ethical principles pronounced in the Declaration of Helsinki (Amendment 64th of the World Medical Association General Assembly, Fortaleza, Brazil, October 2013).
All subjects voluntarily consented prior to enrollment in the study. Each subject enrolled in the study received a copy of his or her signed and dated informed consent and a copy was kept on file at the institution. Significant new study developments were made known to the subjects and documented via a revised informed consent document.

Background therapy:

Interferon alfa-2a (IFN) and interleukin-2 had been standard therapies for patients with mRCC with response rates less than 20% while rather toxic side effects.
The 1st line targeted treatment is dominated by VEGF receptor (VEGFR) tyrosine kinase inhibitors (TKIs) (sunitinib, sorafenib, pazopanib) but also the monoclonal antibody bevacizumab in combination with Interferon. Upon progression on first line, according to all recommendations the standard of therapy should be everolimus.
The role of angiogenesis in the maintenance of solid tumor growth is well established, and the mTOR pathway has been implicated in the regulation of tumor production of proangiogenic factors as well as modulation of VEGFR signaling in endothelial cells.
Everolimus is approved for the treatment of patients with advanced RCC, who progressed during or after treatment with VEGF-targeted therapies. There are cases in everyday practice of patients who are treated with the same agent after been exposed to other agents in between that show antitumor activity. A drug 'holiday' gives the opportunity to transform the cell sensitive to the drug. Recent data have shown that some patients reintroduced to the initial TKI after using another drug are re-sensitized to that TKI.
The aim of this open label randomized phase II study was to explore the efficacy and feasibility of upfront bi-monthly rotations of treatment consisting of 12 weeks of sunitinib 50 mg pd followed by 12 weeks of everolimus 10 mg qd compared to the standard regimen of sunitinib (50 mg qd) until progression, followed thereafter by everolimus (10 mg pd continuously) until progression.

The proposed model was based on data from sunitinib studies which showed that usually maximum response with sunitinib is achieved within about 80 to 90 days from initiation of therapy. So, alternating the drugs every 12 weeks allows maximum effect of the agents and at the same time not allowing resistance mechanisms to emerge.

Evidence for comparator:

Treatment duration did not have a specific period. Patients in the rotational arm received the alternating study regimen until disease progression as defined by RECIST 1.1, until unacceptable toxicity was observed, or patient withdrew for any other reason. In the comparative arm patients received standard

regimen of sunitinib until progression, followed by everolimus until progression.
No other anticancer medication allowed to be used unless a patient had progressed on the rotational arm or after the everolimus treatment on the standard arm
Patients received prescribed (commercial drug) for the first 3 months (until 1st tumor evaluation) and then the patients who were randomized to the control arm were kept receiving commercial (prescribed) drug for both line of therapies (i.e. sunitinib first line and everolimus second line) which were dispensed under the responsibility of Pharmacy Services from the applicable sites according to the applicable regulations for commercial drugs under hospital use. To guarantee the traceability of the drug´s dispensed the following information was registered= commercial name, quantity and batch dispensed to each subject. Patients in the investigational arm received investigational drug provided by Novartis which were dispensed under the responsibility of Pharmacy Services from the applicable sites. The quantity and batches dispensed to each subject were also registered.
Patients were treated with study medications until tumor progression, unacceptable toxicity, death, or discontinuation from the study for any other valid reason.

Actual start date of recruitment	02 July 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 22
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Greece: 11
Worldwide total number of subjects	41
EEA total number of subjects	41

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	25
From 65 to 84 years	16
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Forty-one subjects were enrolled in the study, 26 in an experimental arm and 15 in a control arm. Seven subjects withdrew consent (three at the experimental arm that was 11,5% and none from the control arm).

Pre-assignment

Screening details:

The study was planned for 20 EU sites – 11 in Spain, 5 in France, 3 in Greece and 1 in Italy. Ten sites have recruited at least 1 subject with 1 site (Alexandra General Hospital of Athens) recruited 11 subjects that was about 27% of study population before the study was prematurely terminated.

Period 1

Period 1 title	Baseline period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

All CT/MRIs scans, brain MRIs or CT scans, and bone scans obtained on all patients enrolled at the center were reviewed by the local radiologist who together with the local investigator determined the local assessment of response and progression.
The local radiologist was blinded to the patient's treatment assignment.

Arms

Are arms mutually exclusive?	Yes
Arm title	Experimental arm

Arm description:

In the experimental arm, alternating treatment consisted of repeating cycles of 24 weeks of treatment consisting of 12 weeks of sunitinib 4weeks on 2 weeks off, 50 mg pd followed by 12 weeks of everolimus 10 mg per day 11 weeks on 1 week off in patients with metastatic clear cell renal cancer.

Arm type	Experimental
Investigational medicinal product name	Sunitinib
Investigational medicinal product code	Sunitinib
Other name	Sutent
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

12 weeks of sunitinib 4weeks on 2 weeks off, 50 mg pd

Investigational medicinal product name	Everolimus
Investigational medicinal product code	Everolimus
Other name	Affinitor
Pharmaceutical forms	Pastille
Routes of administration	Oral use

Dosage and administration details:

12 weeks of everolimus 10 mg per day 11 weeks on 1 week off

Arm title	Control arm

Arm description:

sunitinib (50 mg pd 4/2) until progression, followed thereafter by everolimus (10 mg per day continuously) until progression.

Arm type	Active comparator

Investigational medicinal product name	Sunitinib
Investigational medicinal product code	Sunitinib
Other name	Sutent
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

The comparative arm was the standard regimen of sunitinib (50 mg pd 4/2) until progression, followed thereafter by everolimus (10 mg per day continuously) until progression.

Investigational medicinal product name	Everolimus
Investigational medicinal product code	Everolimus
Other name	Affinitor
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

The comparative arm was the standard regimen of sunitinib (50 mg pd 4/2) until progression, followed thereafter by everolimus (10 mg per day continuously) until progression.

Number of subjects in period 1	Experimental arm	Control arm
Started	26	15
Completed	26	15

Baseline characteristics

Reporting groups	
Reporting group title	Experimental arm
Reporting group description:	
In the experimental arm, alternating treatment consisted of repeating cycles of 24 weeks of treatment consisting of 12 weeks of sunitinib 4weeks on 2 weeks off, 50 mg pd followed by 12 weeks of everolimus 10 mg per day 11 weeks on 1 week off in patients with metastatic clear cell renal cancer.	
Reporting group title	Control arm
Reporting group description:	
sunitinib (50 mg pd 4/2) until progression, followed thereafter by everolimus (10 mg per day continuously) until progression.	

Reporting group values	Experimental arm	Control arm	Total
Number of subjects	26	15	41
Age categorical			
Mean age was 60,05 years for overall study population (59,35 for the experimental arm and 61,27 for the control arm). The youngest patient was at his age of 34 and the oldest one at 77 years.			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	16	9	25
From 65-84 years	10	6	16
85 years and over	0	0	0
Age continuous			
Mean age was 60,05 years for overall study population (59,35 for the experimental arm and 61,27 for the control arm). The youngest patient was at his age of 34 and the oldest one at 77 years.			
Units: years			
median	59.5	60	
standard deviation	± 9.59	± 11.4	-
Gender categorical			
Units: Subjects			
Female	4	3	7
Male	22	12	34

End points

End points reporting groups

Reporting group title	Experimental arm

Reporting group description:

In the experimental arm, alternating treatment consisted of repeating cycles of 24 weeks of treatment consisting of 12 weeks of sunitinib 4weeks on 2 weeks off, 50 mg pd followed by 12 weeks of everolimus 10 mg per day 11 weeks on 1 week off in patients with metastatic clear cell renal cancer.

Reporting group title	Control arm

Reporting group description:

sunitinib (50 mg pd 4/2) until progression, followed thereafter by everolimus (10 mg per day continuously) until progression.

Primary: Progression free survival at one year

End point title	Progression free survival at one year

End point description:

-For patients in the "experimental" arm, PFS is defined as the time from the randomization date to objective tumor progression or death due to any cause (whichever occurs first). For PFS analysis, patients who had not progressed and are still alive at the time of data analysis, will be censored at the date of last tumor assessment. Patients with undocumented clinical progression, change of cancer treatment, will be censored at the last tumor assessment date.
-For patients in the "Control" arm, PFS is defined as the time from the randomization date to objective tumor progression after the everolimus treatment start date or death due to any cause (whichever occurred first). For patients who progressed during the sunitinib treatment and were not candidates to be treated with everolimus, PFS was computed as the time from randomization date to this first progression date.

End point type	Primary

End point timeframe:

The primary efficacy endpoint is Progression-free survival (PFS), in terms of PFS rate at 1 year, in each arm.

End point values	Experimental arm	Control arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	15		
Units: events	50	85		

Statistical analyses

Statistical analysis title	Primary endpoint

Statistical analysis description:

No formal comparison was foreseen in this trial between investigational and control arm.
The Simon's design, employed only for the investigation drug, is a within arm design, with the efficacy cut-off defined as at least 36 progression-free survival patients at 12 months out of 68 treated patients, to conclude in favor of the drug. For both arms PFS rated at 12 months were presented with 95% CIs.

Comparison groups	Experimental arm v Control arm

Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.05
Method	Chi-squared corrected

Primary: Progression free survival

End point title	Progression free survival

End point description:

PFS is defined as the time from the randomization date to objective tumor progression or death due to any cause

End point type	Primary

End point timeframe:

PFS is defined as the time from the randomization date to objective tumor progression or death due to any cause

End point values	Experimental arm	Control arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26[1]	15[2]		
Units: months	10	25		

Notes:

[1] - Experimental arm

[2] - Control arm

Statistical analyses

Statistical analysis title	Statistical considerations

Statistical analysis description:

The primary objective of this study was to assess whether the rotational arm has anti-tumor activity, higher than the standard arm. The primary endpoint was the progression-free survival rate at 1 year in each arm.
Simon’s Optimum two stage design was used for the investigational arm with 80% power to demonstrate an increase in 1-year PFS rate to 58% compared to 43% in the control arm.

No formal design was employed for the standard arm.

Comparison groups	Experimental arm v Control arm
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.05
Method	Chi-squared
Parameter estimate	Median difference (final values)
Point estimate	22
Confidence interval	
level	95 %
sides	2-sided
lower limit	6
upper limit	27

Variability estimate	Standard deviation
Dispersion value	0.1123

Notes:

[3] - Primary Analysis:
No formal comparison was foreseen in this trial between investigational and control arm.
The Simon’s design, employed only for the investigation drug, is a within arm design, with the efficacy cut-off defined as at least 36 progression-free survival patients at 12 months out of 68 treated patients, to conclude in favor of the drug. For both arms PFS rated at 12 months were presented with 95% CIs.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The safety summary include only assessments collected no later than 28 days after study treatment discontinuation.

Adverse event reporting additional description:

For the statistical tables, adverse events have been coded according to the Medical Dictionary of Regulatory Activities (MedDRA 19.1) system. Their intensity has been coded by (NCI-CTCAE) v4.0 toxicity criteria.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Experimental arm

Reporting group description:

In the experimental arm, alternating treatment consisted of repeating cycles of 24 weeks of treatment consisting of 12 weeks of sunitinib 4weeks on 2 weeks off, 50 mg pd followed by 12 weeks of everolimus 10 mg per day 11 weeks on 1 week off in patients with metastatic clear cell renal cancer.

Reporting group title	Control arm

Reporting group description:

sunitinib (50 mg pd 4/2) until progression, followed thereafter by everolimus (10 mg per day continuously) until progression.

Serious adverse events	Experimental arm	Control arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 26 (15.38%)	5 / 15 (33.33%)	
number of deaths (all causes)	12	6	
number of deaths resulting from adverse events	0	0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised oedema			
subjects affected / exposed	1 / 26 (3.85%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			

subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 26 (3.85%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory distress			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pneumonitis			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess soft tissue			
subjects affected / exposed	1 / 26 (3.85%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 26 (3.85%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Experimental arm	Control arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 26 (100.00%)	15 / 15 (100.00%)	
Investigations			
Blood triglycerides increased			
subjects affected / exposed	6 / 26 (23.08%)	0 / 15 (0.00%)	
occurrences (all)	6	0	
Blood cholesterol increased			
subjects affected / exposed	6 / 26 (23.08%)	0 / 15 (0.00%)	
occurrences (all)	6	0	
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 26 (15.38%)	1 / 15 (6.67%)	
occurrences (all)	4	1	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	4 / 26 (15.38%)	3 / 15 (20.00%)	
occurrences (all)	4	3	
Blood and lymphatic system disorders			
anaemia			
subjects affected / exposed	8 / 26 (30.77%)	5 / 15 (33.33%)	
occurrences (all)	8	5	
Neutropenia			
subjects affected / exposed	9 / 26 (34.62%)	3 / 15 (20.00%)	
occurrences (all)	9	3	
Thrombocytopenia			
subjects affected / exposed	5 / 26 (19.23%)	2 / 15 (13.33%)	
occurrences (all)	5	2	
General disorders and administration site conditions			
Mucosal inflammation			
subjects affected / exposed	14 / 26 (53.85%)	7 / 15 (46.67%)	
occurrences (all)	14	7	
Eye disorders			
Eyelid oedema			
subjects affected / exposed	2 / 26 (7.69%)	2 / 15 (13.33%)	
occurrences (all)	2	2	
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	13 / 26 (50.00%)	7 / 15 (46.67%)	
occurrences (all)	13	7	
Nausea			
subjects affected / exposed	5 / 26 (19.23%)	7 / 15 (46.67%)	
occurrences (all)	5	7	
Vomiting			
subjects affected / exposed	3 / 26 (11.54%)	2 / 15 (13.33%)	
occurrences (all)	3	2	
Stomatitis			
subjects affected / exposed	3 / 26 (11.54%)	2 / 15 (13.33%)	
occurrences (all)	3	2	
Abdominal pain			
subjects affected / exposed	3 / 26 (11.54%)	1 / 15 (6.67%)	
occurrences (all)	3	1	
Constipation			
subjects affected / exposed	2 / 26 (7.69%)	2 / 15 (13.33%)	
occurrences (all)	2	2	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	1 / 26 (3.85%)	3 / 15 (20.00%)	
occurrences (all)	1	3	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	7 / 26 (26.92%)	3 / 15 (20.00%)	
occurrences (all)	7	3	
Hypertriglyceridaemia			
subjects affected / exposed	8 / 26 (30.77%)	0 / 15 (0.00%)	
occurrences (all)	8	0	
Hyperglycaemia			
subjects affected / exposed	8 / 26 (30.77%)	0 / 15 (0.00%)	
occurrences (all)	8	0	
Hyperuricaemia			
subjects affected / exposed	5 / 26 (19.23%)	1 / 15 (6.67%)	
occurrences (all)	5	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 October 2016	Premature study discontinuation. The Sponsor of the study decided to prematurely close the study, due to the following main reasons: 1. Change in the paradigm on advanced RCC treatment since study initiation (results from the EVERSUN study, published in ASCO 2014, and the new therapies in clear cell RCC, such as commercial pazopanib and nivolumab competitive clinical trials), and although all measures taken by the Sponsor during the trial to try to overtake this situation, has led to a drastic decrease in recruitment rate (only 3 patients randomized during 2016 // 6 patients over the last 12 months of enrolment; below you'll find a graph summarizing this trend since study initiation). 2. This delay in recruitment has drastically increased the costs of the study, due to enrolment staggering, especially with regards to medication supplying for experimental arm (sunitinib costs) 3. Mainly due to the reasons specified in the first point above, the study concept is no longer attractive for the participating investigators, who rather prefer to manage patients according to newer standard of care practice and treatment paradigms, or with other treatments combinations. Available data for all included patients will be captured till 30-Dec-2016 (predicted LPLV), and a descriptive analysis will be performed with data obtained up to this moment. All patients still on active treatment at the time of study discontinuation will be permanently discontinued from the study, being managed from this point onwards at investigators' discretion, and according to the standard of care (SoC) practice. No data will be collected for the purposes of the study from 30-Dec-2016 onwards.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

30 December 2016	The Sponsor of the study decided to prematurely close the study, due to the following main reasons: 1. Change in the paradigm on advanced RCC treatment since study initiation (results from the EVERSUN study, published in ASCO 2014, and the new therapies in clear cell RCC, such as commercial pazopanib and nivolumab competitive clinical trials), and although all measures taken by the Sponsor during the trial to try to overtake this situation, has led to a drastic decrease in recruitment rate (only 3 patients randomized during 2016 // 6 patients over the last 12 months of enrolment; below you'll find a graph summarizing this trend since study initiation). 2. This delay in recruitment has drastically increased the costs of the study, due to enrolment staggering, especially with regards to medication supplying for experimental arm (sunitinib costs) 3. Mainly due to the reasons specified in the first point above, the study concept is no longer attractive for the participating investigators, who rather prefer to manage patients according to newer standard of care practice and treatment paradigms, or with other treatments combinations. Available data for all included patients will be captured till 30-Dec-2016 (predicted LPLV), and a descriptive analysis will be performed with data obtained up to that moment.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Provided the sample size was below than expected as the study was terminated prematurely there was no statistical significance in PFS difference between two arms. However, there was a trend observed favoring the control arm.

Notes: