Clinical trial results:
An open label, single arm trial to characterize patients with metastatic renal cell carcinoma treated with everolimus after failure of the first VEGF-targeted therapy.

Summary

EudraCT number	2010-021370-11
Trial protocol	DE
Global end of trial date	26 September 2017

Results information

Result version number	v1 (current)
This version publication date	15 July 2018
First version publication date	15 July 2018
Summary attachment (see zip file)	MARC-2 Synopsis (MARC2_CSR_FINAL_1.0_20180427_Synopsis_EudraCT.pdf)

Trial information

Trial identification

Sponsor protocol code	CRAD001LDE36T

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01266837
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	iOMEDICO AG
Sponsor organisation address	Hanferstr. 28, Freiburg, Germany, 79108
Public contact	iOMEDICO AG, iOMEDICO AG, 0049 076115242-0, info@iomedico.com
Scientific contact	iOMEDICO AG, iOMEDICO AG, 0049 076115242-0, info@iomedico.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	12 March 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 September 2017
Global end of trial reached?	Yes
Global end of trial date	26 September 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to assess the rate of patients who are free of disease progression after 6 months of treatment with everolimus.

Protection of trial subjects:

The informed consent form (ICF) of patient was obtained in accordance with a) §40 I 3 No. Lit. b) II 1 AMG and §40 I 3 No. 3 Lit. c) IIa 1&2 AMG by the investigator prior to inclusion of each patient into the study.
The nature, objective and consequences of the study, the possible benefits and disadvantages or risks, and the study procedures were explained to each patient orally and in writing. The patients were informed that their participation was voluntary, that they were free to withdraw from the study at any time, and that choosing not to participate would not impact the patient's care or future treatment.
The patients were also informed that, by signing the ICF, they explicitly permitted authorized representatives of the sponsor and the regulatory authorities to access study-related personal data to the extent permitted by the applicable law(s) and/or regulations without violating the confidentiality of the patient to the extent permitted by the applicable law(s) and/or regulations. The patients were also informed that their consent to access their data might not be revoked.
Each patient was given sufficient time to read and discuss the ICF with the investigator prior to giving his/her written consent. Before entry to the study and prior to the conduct of any study-related procedure consent was recorded by means of the patient's dated signature. The patient was then given a copy of the information sheet and his/her signed consent form.
Only eligbile patients were included into this study.
Safety assessments consisted of monitoring and recording of (serious) adverse events until 30 days after the end of treatment and regular monitoring of hematology, blood chemistry, vital signs and physical condition during treatment phase.
Dose adjustments were permitted for patients who did not tolerate dosing as per protocol.

Background therapy:

not applicable

Evidence for comparator:

not applicable

Actual start date of recruitment	21 March 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 63

Worldwide total number of subjects	63
EEA total number of subjects	63

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)	31
From 65 to 84 years	32
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Each patient in the study is uniquely identified by a pseudonymeized patient number which was generated automatically by entering the patient data in the edc. The investigational site had to send a recruiting fax to the sponsor iOMEDICO AG including the edc number immediately after patient enrollment.

Pre-assignment

Screening details:

In a screening period of ≤30 days prior start of everolimus treatment, inclusion and exclusion criteria were checked and screening procedures performed. To determine eligibility the patient's medical records, present clinical and laboratory findings and current tumor status according to RECIST have been assessed.

Pre-assignment period milestones

Number of subjects started	70[1]
Number of subjects completed	63

Pre-assignment subject non-completion reasons

Reason: Number of subjects	no therapy received: 7

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 70 patients have been screened, but only 63 patients started treatment. Only these patients (63) have been specified as "enrolled"

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

not applicable

Arms

Arm title	Everolimus Treatment (FAS)

Arm description:

As recommended per at the time of trial conduction valid SmPC, enrolled patients were to be treated with an initial start dose of 10 mg everolimus (Afinitor®) per os once daily as per current version of SmPC. One cycle consisted of 28 days of continuous administration. A patient was to be treated until documented disease progression according to RECIST version 1.1, unacceptable toxicity, or discontinuation from treatment for any other reason.

Arm type	Experimental
Investigational medicinal product name	Everolimus
Investigational medicinal product code	RAD-001
Other name	Afinitor (R)
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Everolimus, the study drug, was used as commercially available, formulated tablets of 10 mg strength, and 2.5 mg and 5 mg strength for dose modifications, respectively. The study drug was available on prescription by the treating physician.

Number of subjects in period 1	Everolimus Treatment (FAS)
Started	63
Completed	44
Not completed	19
Consent withdrawn by subject	2
Physician decision	4
Adverse event, non-fatal	7
Treat ment end due to patient´s wish	4
patient died	2

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial (overall period)
Reporting group description:	
Reporting group = Full Analysed Set: The FAS comprised all enrolled patients having received at least one dose of everolimus. The FAS was the relevant analysis population used in all efficacy evaluations Safety population: Safety evaluation was performed on the SAF population (N=63) comprising all patients having received at least one dose of everolimus and for whom one further post-baseline information was available.	

Reporting group values	Overall trial (overall period)	Total	
Number of subjects	63	63	
Age categorical Units: Subjects			
Adults (18-64 years)	31	31	
From 65-84 years	32	32	
85 years and over	0	0	
Age continuous Units: years			
median	65.4		
full range (min-max)	43.3 to 81.1	-	
Gender categorical Units: Subjects			
Female	15	15	
Male	48	48	
Site of Tumor Units: Subjects			
Both kidneys	3	3	
Left kidney	28	28	
Right kidney	31	31	
Unknown	1	1	
ECOG Performance Status Units: Subjects			
ECOG 0	36	36	
ECOG 1	25	25	
ECOG 2	2	2	
Tumor size (T) at initial diagnosis Units: Subjects			
T1	18	18	
T2	5	5	
T3	29	29	
T4	4	4	
TX	7	7	
Tumor size (T) at enrolment Units: Subjects			
T0	7	7	
T1	13	13	
T2	1	1	

T3	20	20	
T4	3	3	
Tx	19	19	
Nodal status (N) at initial diagnosis Units: Subjects			
N0	19	19	
N1	3	3	
N2	2	2	
N3	1	1	
NX	38	38	
Nodal status (N) at enrolment Units: Subjects			
N0	18	18	
N1	7	7	
N2	6	6	
N3	2	2	
NX	30	30	
Metastases (M) at initial diagnosis Units: Subjects			
M0	17	17	
M1	24	24	
MX	22	22	
Metastases (M) at enrolment Units: Subjects			
M1	63	63	
AJCC stage at initial diagnosis			
Stage calculated according to AJCC 7th edition, 2010			
Units: Subjects			
Stage I	3	3	
Stage II	3	3	
Stage III	2	2	
Stage IV	24	24	
Missing	31	31	
AJCC stage at enrolment			
Stage calculated according to AJCC 7th edition, 2010			
Units: Subjects			
Stage IV	63	63	
Histology Units: Subjects			
Predominantly clear cell	62	62	
Other (no spec available)	1	1	
BMI at screening Units: kg/m2			
median	26.2		
full range (min-max)	20.3 to 38.1	-	
Time from initial diagnosis to date of informed consent			
For 9 patients of FAS (8 of PP) only the year of the primary diagnosis is known. Date of primary diagnosis is set to 1st of July of the respective year for these cases			
Units: months			
median	44.0		
full range (min-max)	4.8 to 383.1	-	

Time from initial diagnosis to first palliative treatment Units: months median full range (min-max)	 15.0 0.0 to 344.2	 -	
Time from progression on/after first (palliative) VEGFR therapy to date of informed consent Units: months median full range (min-max)	 0.5 0.0 to 12.5	 -	

Subject analysis sets

Subject analysis set title	Per-Protocol Population (PP)
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol (PP) population consists of all patients of the FAS
- without any major protocol deviations (failure of any inclusion / exclusion criteria, no tumor assessment until day 182)
- who have completed the minimum exposure requirement of having a relative dose intensity over the first 2 cycles of treatment of at least 50%.

However, if a patient progressed, discontinued for adverse event or died before the minimum exposure requirement could be met, or before he/she could become evaluable for efficacy, that patient will still be included in the PP Set.
If the numbers of patients in the PP population is more than 10% smaller than the number of patients in the FAS, the demographic and other baseline data will also be summarized descriptively for the PP population. Also a supportive analysis of the primary and secondary objectives will be performed on the basis of the PP population.

Subject analysis set title	Full Analysis (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS comprised all enrolled patients having received at least one dose of everolimus. The FAS was the relevant analysis population used in all efficacy evaluations including demographic and other baseline characteristics as well as study treatment evaluations.

Reporting group values	Per-Protocol Population (PP)	Full Analysis (FAS)	
Number of subjects	49	63	
Age categorical Units: Subjects			
Adults (18-64 years)	23	31	
From 65-84 years	26	32	
85 years and over	0	0	
Age continuous Units: years			
median	66.8	65.4	
full range (min-max)	43.3 to 81.1	43.3 to 81.1	
Gender categorical Units: Subjects			
Female	9	15	
Male	40	48	
Site of Tumor Units: Subjects			
Both kidneys	3	3	
Left kidney	19	28	

Right kidney	26	31	
Unknown	1	1	
ECOG Performance Status Units: Subjects			
ECOG 0	30	36	
ECOG 1	18	25	
ECOG 2	1	2	
Tumor size (T) at initial diagnosis Units: Subjects			
T1	15	18	
T2	3	5	
T3	20	29	
T4	4	4	
TX	7	7	
Tumor size (T) at enrolment Units: Subjects			
T0	4	7	
T1	11	13	
T2	1	1	
T3	15	20	
T4	3	3	
Tx	15	19	
Nodal status (N) at initial diagnosis Units: Subjects			
N0	14	19	
N1	2	3	
N2	2	2	
N3	1	1	
NX	30	38	
Nodal status (N) at enrolment Units: Subjects			
N0	14	18	
N1	4	7	
N2	4	6	
N3	2	2	
NX	25	30	
Metastases (M) at initial diagnosis Units: Subjects			
M0	11	17	
M1	20	24	
MX	18	22	
Metastases (M) at enrolment Units: Subjects			
M1	49	63	
AJCC stage at initial diagnosis			
Stage calculated according to AJCC 7th edition, 2010			
Units: Subjects			
Stage I	3	3	
Stage II	1	3	
Stage III	2	2	
Stage IV	20	24	

Missing	23	31	
AJCC stage at enrolment			
Stage calculated according to AJCC 7th edition, 2010			
Units: Subjects			
Stage IV	49	63	
Histology Units: Subjects			
Predominantly clear cell	49	62	
Other (no spec available)	0	1	
BMI at screening Units: kg/m2			
median	26.9	26.2	
full range (min-max)	20.8 to 37.8	20.3 to 38.1	
Time from initial diagnosis to date of informed consent			
For 9 patients of FAS (8 of PP) only the year of the primary diagnosis is known. Date of primary diagnosis is set to 1st of July of the respective year for these cases			
Units: months			
median	37.8	44.0	
full range (min-max)	4.8 to 383.1	4.8 to 383.1	
Time from initial diagnosis to first palliative treatment Units: months			
median	14.4	15.0	
full range (min-max)	0.0 to 344.2	0.0 to 344.2	
Time from progression on/after first (palliative) VEGFR therapy to date of informed consent Units: months			
median	0.5	0.5	
full range (min-max)	0.0 to 12.5	0.0 to 12.5	

End points

End points reporting groups

Reporting group title	Everolimus Treatment (FAS)

Reporting group description:

As recommended per at the time of trial conduction valid SmPC, enrolled patients were to be treated with an initial start dose of 10 mg everolimus (Afinitor®) per os once daily as per current version of SmPC. One cycle consisted of 28 days of continuous administration. A patient was to be treated until documented disease progression according to RECIST version 1.1, unacceptable toxicity, or discontinuation from treatment for any other reason.

Subject analysis set title	Per-Protocol Population (PP)
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol (PP) population consists of all patients of the FAS
- without any major protocol deviations (failure of any inclusion / exclusion criteria, no tumor assessment until day 182)
- who have completed the minimum exposure requirement of having a relative dose intensity over the first 2 cycles of treatment of at least 50%.

However, if a patient progressed, discontinued for adverse event or died before the minimum exposure requirement could be met, or before he/she could become evaluable for efficacy, that patient will still be included in the PP Set.
If the numbers of patients in the PP population is more than 10% smaller than the number of patients in the FAS, the demographic and other baseline data will also be summarized descriptively for the PP population. Also a supportive analysis of the primary and secondary objectives will be performed on the basis of the PP population.

Subject analysis set title	Full Analysis (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS comprised all enrolled patients having received at least one dose of everolimus. The FAS was the relevant analysis population used in all efficacy evaluations including demographic and other baseline characteristics as well as study treatment evaluations.

Primary: 6-month PFS rate

End point title	6-month PFS rate[1]

End point description:

The primary objective was the assessment of rate of patients who were free of disease progression after 6 months of treatment with everolimus (Kaplan-Meier method for estimating PFS). PFS: time interval between start of everolimus treatment and event / documented event / caesura because of disease progression or death.
For 3 patients in FAS (1 in PP) symptomatic deterioration led to treatment discontinuation. These deteriorations were considered as event for PFS analysis.
Final result: 6 months PFS rate [n%, [95%-CI])]: 39.3% (27.0% - 51.3%) (FAS) bzw. 44.6% (30.0% - 58.2%) (PP)
Results of predefined subgroup analysis (FAS):
- Patient aged ≥65 year: 54.4% (35.2% - 70.1%), Patient aged < 65 year: 23.7% (10.5% - 39.9%)
- Male Pat. : 42.2% (27.9% - 55.9%) female Pat.: 45.8% (29.6% - 60.6%)
- Patients with BMI >25kg/m² 51.4% (34.7% - 65.7%), Pat. With BMI ≤25kg/m² 18.2% (5.7% - 36.3%)
- Patients with ECOG 0: 41.6% (25.0% - 57.5%) Patients with ECOG ≥1: 37.0% (19.6% - 54.6%)

End point type	Primary

End point timeframe:

Time from first day of intake of everolimus until disease progression or death of any cause.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Sample size calculation was based on the width of 95% confidence levels of 6-month PFS rate. Therefore no statistical analysis but for calculation of 95% confidence limits was conducted

End point values	Everolimus Treatment (FAS)	Per-Protocol Population (PP)	Full Analysis (FAS)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	63	49	63	
Units: Percentage of patients				
number (confidence interval 95%)	39.3 (27.0 to 51.3)	44.6 (30.0 to 58.2)	39.3 (27.0 to 51.3)	

Attachments (see zip file)	6-Months PFS Rate - Subgroups.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)

End point description:

The Kaplan-Meier product-limit method was used to describe PFS (median, 95% confidence intervals, and plots). PFS was analyzed at the final analysis cut-off date and was also be calculated for each stratum defined by the result of prior TKI-treatment.
Final result: The median PFS (median, months) [95% CI] was: 3.8 (3.2 - 6.2) (FAS) resp. 5.3 (3.2 - 8.1) (PP)
Results of predefined subgroup analysis (FAS) were:
Patient aged ≥65 year: 6.9 (3.7 - 9.4), Patient aged < 65 year: 3.2 (1.7 - 3.8)
Male Pat: 4.0 (3.2 - 8.1), female Pat: 3.6 (1.1 - 6.2)
Patients with BMI >25kg/m²: 6.2 (3.6 - 8.4), Pat. with BMI ≤25kg/m²: 2.2 (1.6 - 4.7)
Patients with ECOG 0: 3.8 (2.0 - 9.3), Patients with ECOG ≥1: 7.8 (5.6 - 22.1)

End point type	Secondary

End point timeframe:

PFS is defined as the time interval between start of everolimus treatment and event / documented event / Caesura because ofdisease progression or death due to any cause. The PFS was estimated by Kaplan-Meier analysis.

End point values	Per-Protocol Population (PP)	Full Analysis (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	49	63		
Units: months				
median (confidence interval 95%)	5.3 (3.2 to 8.1)	3.8 (3.2 to 6.2)		

Attachments (see zip file)	PFS Kaplan-Meier Plot (PP).png PFS Kaplan-Meier Plot (FAS).png Progression Free Survival – Subgroups (FAS; PP)/Progression

Statistical analyses

No statistical analyses for this end point

Secondary: Best Response and Objective Response Rate (ORR)

End point title	Best Response and Objective Response Rate (ORR)

End point description:

Tumor evaluation was assessed acc. to RECIST 1.1. Best response and objective response rate (ORR=CR [Complete Remission] + PR [Partial Remission]) were calculculated and summarized in terms Patient numbers and of percentage rates.
Final result: The overall Response rate (number of patients (%)) was: 5 (7.9%) (FAS) resp. 4 (8.2%) (PP)
Results of predefined subgroup analysis (FAS) were:
Patient aged ≥65 year: 3 (9.4%), Patient aged < 65 year: 2 (6.5%)
Male Pat: 4 (8.3%), female Pat: 1 (6.7%)
Patients with BMI >25kg/m²: 4 (9.8%), Pat. With BMI ≤25kg/m²: 1 (4.5%)
Patients with ECOG 0: 5 (13.9%), Patients with ECOG ≥1: 0
Missing / not done: response never evaluated. For 1 patient in PP response was never evaluated (Patient ID 10003). Nevertheless, this patient is not excluded from PP since he died about 4 months after date of informed consent. CR = complete remission; PR = partial remission; SD = stable disease; PD = progressive disease; NE = not evaluable;

End point type	Secondary

End point timeframe:

Time from baseline (up to 30 days prior to the first intake of study medication) until progressive disease. Patients alive at the end of observation time were right-censored at the date of last contact.

End point values	Per-Protocol Population (PP)	Full Analysis (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	49	63		
Units: number				
CR	0	0		
PR	4	5		
Overall Response (CR+PR)	4	5		
SD	27	33		
PD	16	21		
NE	1	1		
Missing / not done	1	3		

Attachments (see zip file)	Best Response and ORR - Subgroups/Best Response and

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

OS was determined using the method of Kaplan-Meier. During the course of the study, death was documented in 45 (71.4%) and 32 (65.3%) patients in the FAS and PP population, respectively.
Final result: The median OS (months) [95% CI] was: 16.8 (14.3 - 24.3) (FAS) resp. 22.9 (15.8 - 36.1)

(PP)
Results of predefined subgroup analysis (FAS) were:
Patient aged ≥65 year: 24.3 (14.0 - 47.9), Patient aged < 65 year: 16.3 (8.9 - 21.8)
Male Pat: 4.0 20.4 (14.3 - 36.1), female Pat: 16.3 (5.1 - 21.8)
Patients with BMI >25kg/m²: 24.3 (16.8 - 47.9), Pat. With BMI ≤25kg/m²: 12.0 (4.0 - 15.8)
Patients with ECOG 0: 24.1 (15.8 - 59.7), Patients with ECOG ≥1: 10.8 (6.8 - 22.9)

End point type	Secondary

End point timeframe:

Overall survival is defined as time from first administration of everolimus to death due to any cause. Data of patients alive at the end of observation time were right-censored at the date of last contact.

End point values	Per-Protocol Population (PP)	Full Analysis (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	49	63		
Units: months				
median (confidence interval 95%)	22.9 (15.8 to 36.1)	16.8 (14.3 to 24.3)		

Attachments (see zip file)	OS Kaplan-Meier Plot (FAS).png OS-Subgroups/Overall Survival - Subgroups.docx OS Kaplan-Meier Plot (PP).png

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs, SAEs and fatal SAEs (regardless of causality) were collected from the intake of the first dose of everolimus until 30 days after the last intake, even if the event is not considered to be related to everolimus.

Adverse event reporting additional description:

Treatment-emergent AEs (TEAEs) overall and as characterized by CTCAE severity grade, MedDRA (Medical Dictionary for Regulatory Activities) classified SOC (System Organ Class) and PT (Preferred Term). An AE was classified as drug-related if the relationship was classified as "related to everolimus" by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Everolimus treatment

Reporting group description:

SAF: Safety evaluation was performed on the SAF population (N=63) comprising all patients having received at least one dose of everolimus and for whom one further post-baseline information was available.

Serious adverse events	Everolimus treatment		
Total subjects affected by serious adverse events			
subjects affected / exposed	31 / 63 (49.21%)		
number of deaths (all causes)	45		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	3 / 63 (4.76%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 3		
Metastases to central nervous system			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Metastases to perineum			

subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tumour pain			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Venous thrombosis			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Cancer surgery			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	2 / 63 (3.17%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Hypersensitivity			

subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease			
subjects affected / exposed	2 / 63 (3.17%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Pneumonitis			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Alanine aminotransferase increased			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Femur fracture			

subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tendon rupture			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thoracic vertebral fracture			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure congestive			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Seizure			
subjects affected / exposed	3 / 63 (4.76%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Monoparesis			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Paresis			

subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 63 (3.17%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Upper gastrointestinal haemorrhage			
subjects affected / exposed	2 / 63 (3.17%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	1 / 1		
Faecaloma			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oesophagitis			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Stomatitis			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Swollen tongue			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Tongue oedema			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			

subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Device related infection			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	2 / 63 (3.17%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Erysipelas			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Otitis externa			

subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Everolimus treatment		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	61 / 63 (96.83%)		
Investigations			
Blood triglycerides increased			
subjects affected / exposed	4 / 63 (6.35%)		
occurrences (all)	9		
Weight decreased			
subjects affected / exposed	4 / 63 (6.35%)		
occurrences (all)	7		
Gamma-glutamyltransferase increased			
subjects affected / exposed	4 / 63 (6.35%)		
occurrences (all)	5		
Nervous system disorders			

Dysgeusia subjects affected / exposed occurrences (all)	10 / 63 (15.87%) 10		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) Oedema peripheral subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all) Pain subjects affected / exposed occurrences (all)	 20 / 63 (31.75%) 26 14 / 63 (22.22%) 19 8 / 63 (12.70%) 9 4 / 63 (6.35%) 4		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	 18 / 63 (28.57%) 23		
Eye disorders Eyelid oedema subjects affected / exposed occurrences (all)	 5 / 63 (7.94%) 6		
Gastrointestinal disorders Stomatitis subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	 19 / 63 (30.16%) 29 10 / 63 (15.87%) 13 9 / 63 (14.29%) 10		
Respiratory, thoracic and mediastinal disorders			

Cough subjects affected / exposed occurrences (all)	15 / 63 (23.81%) 21		
Epistaxis subjects affected / exposed occurrences (all)	17 / 63 (26.98%) 20		
Dyspnoea subjects affected / exposed occurrences (all)	13 / 63 (20.63%) 15		
Pneumonitis subjects affected / exposed occurrences (all)	8 / 63 (12.70%) 13		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	18 / 63 (28.57%) 26		
Pruritus subjects affected / exposed occurrences (all)	13 / 63 (20.63%) 17		
Dry skin subjects affected / exposed occurrences (all)	4 / 63 (6.35%) 5		
Palmar-plantar erythrodysaesthesia syndrome subjects affected / exposed occurrences (all)	4 / 63 (6.35%) 4		
Musculoskeletal and connective tissue disorders Pain in extremity subjects affected / exposed occurrences (all)	4 / 63 (6.35%) 5		
Infections and infestations Paronychia subjects affected / exposed occurrences (all)	4 / 63 (6.35%) 5		
Metabolism and nutrition disorders Decreased appetite			

subjects affected / exposed	13 / 63 (20.63%)		
occurrences (all)	15		
Hyperglycaemia			
subjects affected / exposed	9 / 63 (14.29%)		
occurrences (all)	15		
Hypertriglyceridaemia			
subjects affected / exposed	4 / 63 (6.35%)		
occurrences (all)	8		
Hyperkalaemia			
subjects affected / exposed	4 / 63 (6.35%)		
occurrences (all)	4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 August 2011	Amendment I: Amendment to PIC (Patient Informed Consent) Version 2.0. Reference to package insert of everolimus instead of listing all reported AEs associated with everolimus.
03 April 2012	Amendment to CSP (Clinical Study Protocol) Version 2.0 New adverse events (renal failure and proteinuria); more detailed monitoring of renal function. Addition of translational project.
10 September 2013	Amendment to CSP. Version 3.0 Implementation of changes to the current version of SmPC of everolimus (Afinitor®); dose modification in case of liver function impairment. Prolongation of the recruitment period with 30 months (total 54 months). Cancellation of interim safety analysis.
18 October 2013	Amendment to PIC (Version 3.0). Implementation of changes to current version of SmPC of everolimus; in Chapter 4.6 (Fertility, Pregnancy and Breastfeeding) it was noted that treatment with everolimus may be associated with a limitation of female fertility.
25 August 2016	Amendment to CSP. (Version 4.0) Premature study end. Definition of end of study (Sep 2017). Postponement of the final analysis and addition of an interim analysis. The final analysis (initially planned 8 months after the last patient was included) was changed to an interim analysis. The final analysis was postponed to the end of the study. "The investigation of the relation between biomarkers and clinical benefit" defined as explorative objective and performed independently of the final analysis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported