Clinical trial results:
RAPTOR: A single arm, multicenter phase II trial of RAD001 as monotherapy in the treatment of advanced papillary renal cell cancer

Summary

EudraCT number	2008-006181-28
Trial protocol	FR BE GB DE ES IT
Global end of trial date	13 October 2014

Results information

Result version number	v1 (current)
This version publication date	24 July 2016
First version publication date	24 July 2016

Trial information

Trial identification

Sponsor protocol code	CRAD001LFR08

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,

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	13 October 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 October 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of everolimus as monotherapy in patients with metastatic papillary renal cancer. Efficacy was defined as the percentage of patients progression-free at 6 months.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 July 2009
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	Belgium: 6
Country: Number of subjects enrolled	France: 30
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Italy: 11
Country: Number of subjects enrolled	Poland: 16
Country: Number of subjects enrolled	Spain: 17
Country: Number of subjects enrolled	United Kingdom: 6
Worldwide total number of subjects	92
EEA total number of subjects	92

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)	54
From 65 to 84 years	38
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

All patients were screened for inclusion and exclusion criteria and baseline evaluations were performed within two weeks and up to a maximum of 4 weeks for specific exams, before the first dose of study drug.

Period 1

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

Arms

Arm title	RAD001

Arm description:

10 mg/day

Arm type	Experimental
Investigational medicinal product name	Everolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Chewable/dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

5 mg tablets 10 mg/day

Number of subjects in period 1	RAD001
Started	92
Completed	0
Not completed	92
Adverse event, serious fatal	9
Consent withdrawn by subject	3
Disease progression	55
Adverse event, non-fatal	20
Lost to follow-up	3
Missing	1
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	RAD001
Reporting group description: 10 mg/day	

Reporting group values	RAD001	Total	
Number of subjects	92	92	
Age Categorical Units: participants			
Between 18 and 65 years	54	54	
>=65 years	38	38	
Age Continuous Units: years			
arithmetic mean	59.2		
standard deviation	± 14.9	-	
Gender, Male/Female Units: participants			
Male	72	72	
Female	20	20	

End points

End points reporting groups

Reporting group title	RAD001
Reporting group description:	
10 mg/day	

Primary: To evaluate efficacy of RAD001 as monotherapy for the treatment of papillary renal cancer. Efficacy is defined as the percentage of patients progression-free at 6 months.

End point title	To evaluate efficacy of RAD001 as monotherapy for the treatment of papillary renal cancer. Efficacy is defined as the percentage of patients progression-free at 6 months.[1]
End point description:	
PFSR at 6 months based on central review	
End point type	Primary
End point timeframe:	
6 mos	

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: Only summary stats available as this is a one arm study. EU only provides for comparative statistics.

End point values	RAD001			
Subject group type	Reporting group			
Number of subjects analysed	92			
Units: % participants				
number (confidence interval 80%)				
(PPFF Set, N=44)	34.1 (24.5 to 44.8)			
(PPSet, N=66)	33.3 (25.6 to 41.8)			
(ITT Set, N=86)	32.6 (25.9 to 39.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Disease control rate (SD + PR + CR)

End point title	Disease control rate (SD + PR + CR)
End point description:	
DCR was defined as the proportion of patients with a best overall response of CR, PR or SD and ORR as the percentage of patients with CR or PR	
End point type	Secondary
End point timeframe:	
6 mos	

End point values	RAD001			
Subject group type	Reporting group			
Number of subjects analysed	92			
Units: % Participants				
number (confidence interval 90%)				
PP set	65.2 (54.4 to 74.9)			
ITT set	65.1 (55.8 to 73.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Objective response rate

End point title	Objective response rate

End point description:

ORR is defined as the proportion of patients with tumor size reduction of a predefined amount and for a minimum time period. Response duration usually is measured from the time of initial response until documented tumor progression

End point type	Secondary

End point timeframe:

End of trial

End point values	RAD001			
Subject group type	Reporting group			
Number of subjects analysed	92			
Units: % participants				
number (confidence interval 90%)				
PP Set	1.5 (0.1 to 7)			
ITT Set	1.2 (0.1 to 5.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response

End point title	Duration of response

End point description:

The DOR analysis applied only to patients whose overall response was CR or PR and was defined as the time from onset of response (CR/PR) to progression or death from any cause.

End point type	Secondary

End point timeframe:

End of trial

End point values	RAD001			
Subject group type	Reporting group			
Number of subjects analysed	92			
Units: days				
median (confidence interval 95%)				
local review PP set	169 (64 to 169)			
local review ITT set	226 (64 to 928)			

Statistical analyses

No statistical analyses for this end point

Secondary: Median progression free survival

End point title	Median progression free survival

End point description:

PFS was defined as the time from first study drug administration to objective tumor progression or death from any cause.

End point type	Secondary

End point timeframe:

End of trial

End point values	RAD001			
Subject group type	Reporting group			
Number of subjects analysed	92			
Units: days				
median (confidence interval 95%)				
PP set	118 (65 to 174)			
ITT set	113 (77 to 167)			

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of adverse events, serious adverse events, and death.

End point title	Incidence of adverse events, serious adverse events, and death.

End point description:

End point type	Secondary

End point timeframe:

End of trial

End point values	RAD001			
Subject group type	Reporting group			
Number of subjects analysed	92			
Units: % participants				
number (not applicable)				
Patients with any AE	100			
AE with suspected relation to study drug	97.83			
AE leading to dose adjustment or interruption	53.26			
AE leading to permanent discontinuation	27.17			
AE requiring concomitant medication	90.22			
Patients with serious adverse event (SAE)	46.74			
SAE suspected relation to study drug	23.91			
SAE leading to permanent discontinuation	10.87			
Patients died	10.87			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	All patients

Reporting group description:

All patients

Serious adverse events	All patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	43 / 92 (46.74%)		
number of deaths (all causes)	11		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm progression			
subjects affected / exposed	4 / 92 (4.35%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Varicose vein			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertension			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Deep vein thrombosis			

subjects affected / exposed	2 / 92 (2.17%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Venous thrombosis				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Asthenia				
subjects affected / exposed	4 / 92 (4.35%)			
occurrences causally related to treatment / all	3 / 5			
deaths causally related to treatment / all	0 / 0			
Chest pain				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Condition aggravated				
subjects affected / exposed	2 / 92 (2.17%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Multi-organ failure				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Mucosal inflammation				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
subjects affected / exposed	2 / 92 (2.17%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Oedema peripheral				

subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	4 / 92 (4.35%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Vaginal haemorrhage				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Cough				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Epistaxis				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnoea exertional				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	3 / 92 (3.26%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Lung disorder				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Interstitial lung disease				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Nasal septum deviation				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oropharyngeal pain				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	4 / 92 (4.35%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Pulmonary arterial hypertension				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				

Depression				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hallucination				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Blood creatinine increased				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Lumbar vertebral fracture				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Atrial fibrillation				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atrial flutter				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cor pulmonale				

subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tricuspid valve incompetence			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Aphasia			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hemiparesis			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal cord compression			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tremor			
subjects affected / exposed	1 / 92 (1.09%)		
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	4 / 92 (4.35%)		
occurrences causally related to treatment / all	3 / 4		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	2 / 92 (2.17%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		

Abdominal pain			
subjects affected / exposed	2 / 92 (2.17%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Colitis			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Ileus			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Large intestine polyp			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oesophagitis			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Subileus			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			

Cholestasis			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash erythematous			
subjects affected / exposed	2 / 92 (2.17%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	3 / 92 (3.26%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Renal failure acute			
subjects affected / exposed	4 / 92 (4.35%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bone pain			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fistula			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Anal infection			

subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bacteraemia				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Erysipelas				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal infection				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Herpes zoster				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	2 / 92 (2.17%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Postoperative abscess				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia bacterial				

subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Respiratory tract infection			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 92 (2.17%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Fluid overload			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	All patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	90 / 92 (97.83%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 92 (6.52%)		
occurrences (all)	6		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	39 / 92 (42.39%)		
occurrences (all)	52		
Chest pain			
subjects affected / exposed	7 / 92 (7.61%)		
occurrences (all)	8		
Fatigue			
subjects affected / exposed	30 / 92 (32.61%)		
occurrences (all)	37		
Mucosal inflammation			
subjects affected / exposed	36 / 92 (39.13%)		
occurrences (all)	56		
Oedema peripheral			
subjects affected / exposed	29 / 92 (31.52%)		
occurrences (all)	37		
Pyrexia			
subjects affected / exposed	25 / 92 (27.17%)		
occurrences (all)	33		
Pain			
subjects affected / exposed	7 / 92 (7.61%)		
occurrences (all)	12		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	36 / 92 (39.13%)		
occurrences (all)	47		
Dyspnoea			
subjects affected / exposed	29 / 92 (31.52%)		
occurrences (all)	35		

Epistaxis subjects affected / exposed occurrences (all)	26 / 92 (28.26%) 41		
Pneumonitis subjects affected / exposed occurrences (all)	7 / 92 (7.61%) 7		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	9 / 92 (9.78%) 10		
Investigations Blood creatinine increased subjects affected / exposed occurrences (all)	8 / 92 (8.70%) 9		
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	6 / 92 (6.52%) 9		
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	7 / 92 (7.61%) 10		
Platelet count decreased subjects affected / exposed occurrences (all)	6 / 92 (6.52%) 14		
Weight decreased subjects affected / exposed occurrences (all)	12 / 92 (13.04%) 13		
Cardiac disorders Tachycardia subjects affected / exposed occurrences (all)	6 / 92 (6.52%) 6		
Nervous system disorders Dysgeusia subjects affected / exposed occurrences (all)	23 / 92 (25.00%) 27		
Headache			

subjects affected / exposed	16 / 92 (17.39%)		
occurrences (all)	22		
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	10 / 92 (10.87%)		
occurrences (all)	12		
Anaemia			
subjects affected / exposed	25 / 92 (27.17%)		
occurrences (all)	29		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	23 / 92 (25.00%)		
occurrences (all)	32		
Aphthous stomatitis			
subjects affected / exposed	11 / 92 (11.96%)		
occurrences (all)	16		
Ascites			
subjects affected / exposed	5 / 92 (5.43%)		
occurrences (all)	5		
Constipation			
subjects affected / exposed	15 / 92 (16.30%)		
occurrences (all)	18		
Diarrhoea			
subjects affected / exposed	36 / 92 (39.13%)		
occurrences (all)	52		
Nausea			
subjects affected / exposed	27 / 92 (29.35%)		
occurrences (all)	36		
Dry mouth			
subjects affected / exposed	8 / 92 (8.70%)		
occurrences (all)	8		
Stomatitis			
subjects affected / exposed	23 / 92 (25.00%)		
occurrences (all)	32		
Vomiting			

subjects affected / exposed	16 / 92 (17.39%)		
occurrences (all)	21		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	5 / 92 (5.43%)		
occurrences (all)	5		
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	5 / 92 (5.43%)		
occurrences (all)	5		
Nail disorder			
subjects affected / exposed	13 / 92 (14.13%)		
occurrences (all)	14		
Dry skin			
subjects affected / exposed	12 / 92 (13.04%)		
occurrences (all)	12		
Pruritus			
subjects affected / exposed	20 / 92 (21.74%)		
occurrences (all)	25		
Rash			
subjects affected / exposed	53 / 92 (57.61%)		
occurrences (all)	77		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	11 / 92 (11.96%)		
occurrences (all)	12		
Back pain			
subjects affected / exposed	16 / 92 (17.39%)		
occurrences (all)	21		
Musculoskeletal pain			
subjects affected / exposed	5 / 92 (5.43%)		
occurrences (all)	7		
Pain in extremity			
subjects affected / exposed	10 / 92 (10.87%)		
occurrences (all)	11		
Myalgia			

subjects affected / exposed	5 / 92 (5.43%)		
occurrences (all)	7		
Infections and infestations			
Rhinitis			
subjects affected / exposed	9 / 92 (9.78%)		
occurrences (all)	9		
Bronchitis			
subjects affected / exposed	5 / 92 (5.43%)		
occurrences (all)	5		
Urinary tract infection			
subjects affected / exposed	6 / 92 (6.52%)		
occurrences (all)	8		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	36 / 92 (39.13%)		
occurrences (all)	48		
Hyperglycaemia			
subjects affected / exposed	12 / 92 (13.04%)		
occurrences (all)	12		
Hypercholesterolaemia			
subjects affected / exposed	15 / 92 (16.30%)		
occurrences (all)	20		
Hypertriglyceridaemia			
subjects affected / exposed	10 / 92 (10.87%)		
occurrences (all)	15		
Hypocalcaemia			
subjects affected / exposed	5 / 92 (5.43%)		
occurrences (all)	5		
Hypophosphataemia			
subjects affected / exposed	8 / 92 (8.70%)		
occurrences (all)	10		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 April 2010	Addition of guidelines regarding the management of hepatitis B and hepatitis C infections. Reactivation of hepatitis B virus (HBV) has been observed in patients with cancer receiving chemotherapy (Yeo et al 2004). Sporadic cases of hepatitis B reactivation has also been seen in this setting with everolimus. Use of antivirals treatments during anti-cancer therapy has been shown to reduce the risk of hepatitis B virus reactivation and associated morbidity and mortality (Loomba et al 2008). Guidance on the management of patients at risk of hepatitis C viral reactivation was also provided. Clarification of inclusion criteria n° 9, 10 adding or modifying notes Clarification of exclusion criterion n° 10 adding or modifying notes Addition of exclusion criterion n° 15 Management of hyperglycemia and duration of use of adequate contraception after end of trial therapy to provide a language that was consistent with the most recent Everolimus Core Data Sheet Version 1.3. Updated everolimus safety information based on the updated investigator brochure version 8 (mainly Appendix 16.1.1 - Section 5.1.1.1) Guidance on the usage of CYP3A4 and/or PgP inducers and inhibitors was modified to be consistent with Internal Clinical Pharmacology Drug-drug interaction (DDI) memo, which was updated Dec. 2, 2009. The memo summarized DDI data from three sources including the FDA's "Guidance for Industry, Drug Interaction Studies, the University of Washington's Drug Interaction Database, and Indiana University School of Medicine's Drug Interaction Table." Language regarding the administration of everolimus was modified to administer everolimus after meals in clinical trials. This approach had been approved as the global strategy within the Afinitor (everolimus) Program Team to achieve consistency between the various clinical trials.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported