



Clinical trial results:

An open-label, multicenter phase II study to examine the efficacy and safety of everolimus as second-line therapy in the treatment of patients with metastatic renal cell carcinoma (RECORD-4)

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com/CtrdWeb/home.novfor> complete trial results.

Summary

EudraCT number	2010-020447-13
Trial protocol	BG
Global end of trial date	05 May 2015

Results information

Result version number	v1 (current)
This version publication date	06 July 2018
First version publication date	06 July 2018

Trial information

Trial identification

Sponsor protocol code	CRAD001L2404
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01491672
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 X,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111 X,

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 May 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 May 2015
Global end of trial reached?	Yes
Global end of trial date	05 May 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to assess the progression-free survival (PFS) in patients who received everolimus as second-line treatment for metastatic renal cell carcinoma.

Protection of trial subjects:

This study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical practices 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	30 November 2011
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	United States: 16
Country: Number of subjects enrolled	China: 55
Country: Number of subjects enrolled	Bulgaria: 8
Country: Number of subjects enrolled	Brazil: 8
Country: Number of subjects enrolled	Argentina: 6
Country: Number of subjects enrolled	Russian Federation: 41
Worldwide total number of subjects	134
EEA total number of subjects	8

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)	105
From 65 to 84 years	29
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This was an open-label study where all eligible participants were enrolled into one of 3 cohorts based upon prior first-line therapy.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Prior sunitinib

Arm description:

Participants, who received prior sunitinib therapy, received RAD001 10 mg orally once daily.

Arm type	Experimental
Investigational medicinal product name	RAD001
Investigational medicinal product code	RAD001
Other name	Everolimus
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

10 mg orally once daily

Arm title	Other prior vascular endothelial growth factor (VEGF)
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Arm description:

Participants, who received prior anti-VEGF other than sunitinib, received RAD001 10 mg orally once daily.

Arm type	Experimental
Investigational medicinal product name	RAD001
Investigational medicinal product code	RAD001
Other name	Everolimus
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

10 mg orally once daily

Arm title	Prior cytokines
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Arm description:

Participants, who received prior cytokine therapy, received RAD001 10 mg orally once daily.

Arm type	Experimental
Investigational medicinal product name	RAD001
Investigational medicinal product code	RAD001
Other name	Everolimus
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

10 mg orally once daily

Number of subjects in period 1	Prior sunitinib	Other prior vascular endothelial growth factor (VEGF)	Prior cytokines
Started	58	62	14
Safety set	58	61	14
Completed	2	2	3
Not completed	56	60	11
Adverse event, serious fatal	-	4	-
Consent withdrawn by subject	6	7	-
Disease progression	42	34	6
Adverse event, non-fatal	8	10	4
Protocol deviation	-	1	-
Lost to follow-up	-	4	1

Baseline characteristics

Reporting groups

Reporting group title	Prior sunitinib
Reporting group description:	
Participants, who received prior sunitinib therapy, received RAD001 10 mg orally once daily.	
Reporting group title	Other prior vascular endothelial growth factor (VEGF)
Reporting group description:	
Participants, who received prior anti-VEGF other than sunitinib, received RAD001 10 mg orally once daily.	
Reporting group title	Prior cytokines
Reporting group description:	
Participants, who received prior cytokine therapy, received RAD001 10 mg orally once daily.	

Reporting group values	Prior sunitinib	Other prior vascular endothelial growth factor (VEGF)	Prior cytokines
Number of subjects	58	62	14
Age categorical			
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)	47	49	9
From 65-84 years	11	13	5
85 years and over	0	0	0
Age Continuous			
Units: Years			
arithmetic mean	56	56.5	60.3
standard deviation	± 12.06	± 11.14	± 10.59
Gender, Male/Female			
Units: Participants			
Female	15	22	6
Male	43	40	8

Reporting group values	Total		
Number of subjects	134		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	105		
From 65-84 years	29		
85 years and over	0		
Age Continuous Units: Years arithmetic mean standard deviation	-		
Gender, Male/Female Units: Participants			
Female	43		
Male	91		

End points

End points reporting groups

Reporting group title	Prior sunitinib
Reporting group description: Participants, who received prior sunitinib therapy, received RAD001 10 mg orally once daily.	
Reporting group title	Other prior vascular endothelial growth factor (VEGF)
Reporting group description: Participants, who received prior anti-VEGF other than sunitinib, received RAD001 10 mg orally once daily.	
Reporting group title	Prior cytokines
Reporting group description: Participants, who received prior cytokine therapy, received RAD001 10 mg orally once daily.	
Subject analysis set title	All participants
Subject analysis set type	Full analysis
Subject analysis set description: All participants received RAD001 10 mg daily.	

Primary: Progression-free survival (PFS) - all participants

End point title	Progression-free survival (PFS) - all participants ^[1]
End point description: PFS during second-line treatment was defined as the time from the date of enrollment to the date of the first documented disease progression or death due to any cause. PFS was based on the local radiological data according to the RECIST 1.0 criteria.	
End point type	Primary
End point timeframe: 20 months	

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: No statistical analysis was planned for the primary outcome measure.

End point values	All participants			
Subject group type	Subject analysis set			
Number of subjects analysed	134			
Units: months				
median (confidence interval 95%)	7.4 (5.6 to 10.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of PFS for each first-line treatment cohort

End point title	Duration of PFS for each first-line treatment cohort
End point description: Duration of PFS during second-line treatment was defined as the time from the date of enrollment to the date of the first documented disease progression or death due to any cause. Participants' assessment was based on the local radiological data according to the RECIST 1.0 Criteria.	
End point type	Secondary

End point timeframe:

20 months

End point values	Prior sunitinib	Other prior vascular endothelial growth factor (VEGF)	Prior cytokines	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	58	62	14	
Units: months				
median (confidence interval 95%)	5.6 (3.7 to 11.3)	7.8 (5.7 to 11)	12.9 (2.6 to 999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title	Overall survival (OS)
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End point description:

OS was defined as the time from date of enrollment to date of death due to any cause.

End point type	Secondary
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End point timeframe:

28 months

End point values	Prior sunitinib	Other prior vascular endothelial growth factor (VEGF)	Prior cytokines	All participants
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	58	62	14	134
Units: months				
median (confidence interval 95%)	23.8 (13.7 to 999)	17.2 (11.9 to 999)	99 (15.9 to 999)	23.8 (17 to 999)

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Rate (CBR)

End point title	Clinical Benefit Rate (CBR)
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End point description:

CBR was defined as the proportion of patients with best overall response of complete response (CR) or partial response (PR) or stable disease based on the local radiological data according to the RECIST 1.0 criteria.

End point type	Secondary
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End point timeframe:

20 months

End point values	Prior sunitinib	Other prior vascular endothelial growth factor (VEGF)	Prior cytokines	All participants
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	58	62	14	134
Units: Participants	41	48	11	100

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)
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End point description:

ORR was defined as the proportion of participants with best overall response of CR or PR based on the local radiological data according to the RECIST 1.0 Criteria

End point type	Secondary
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End point timeframe:

20 months

End point values	Prior sunitinib	Other prior vascular endothelial growth factor (VEGF)	Prior cytokines	All participants
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	58	62	14	134
Units: Participants	4	3	3	10

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DoR)

End point title	Duration of Response (DoR)
End point description: DoR was defined as the time from the first occurrence of PR or CR (as per local radiological review) until the date of the first documented disease progression or death due to underlying cancer.	
End point type	Secondary
End point timeframe: 20 months	

End point values	Prior sunitinib	Other prior vascular endothelial growth factor (VEGF)	Prior cytokines	All participants
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	58	62	14	134
Units: months				
median (confidence interval 95%)	10.8 (9.2 to 999)	7.4 (3.3 to 9.2)	9.2 (-999 to 999)	9.2 (3.3 to 999)

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 reported in this record are from date of 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
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Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Prior sunitinib
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Reporting group description:

Prior sunitinib

Reporting group title	Prior cytokines
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Reporting group description:

Prior cytokines

Reporting group title	Other prior anti VEGF
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Reporting group description:

Other prior anti VEGF

Serious adverse events	Prior sunitinib	Prior cytokines	Other prior anti VEGF
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 58 (22.41%)	3 / 14 (21.43%)	16 / 61 (26.23%)
number of deaths (all causes)	4	0	9
number of deaths resulting from adverse events	0	0	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	1 / 58 (1.72%)	0 / 14 (0.00%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal neoplasm			
subjects affected / exposed	1 / 58 (1.72%)	0 / 14 (0.00%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 58 (0.00%)	0 / 14 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis			
subjects affected / exposed	0 / 58 (0.00%)	0 / 14 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Multi-organ failure			
subjects affected / exposed	1 / 58 (1.72%)	0 / 14 (0.00%)	2 / 61 (3.28%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 2
Sudden death			
subjects affected / exposed	0 / 58 (0.00%)	0 / 14 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 58 (1.72%)	0 / 14 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydrothorax			
subjects affected / exposed	0 / 58 (0.00%)	0 / 14 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	1 / 58 (1.72%)	0 / 14 (0.00%)	2 / 61 (3.28%)
occurrences causally related to treatment / all	1 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			

subjects affected / exposed	0 / 58 (0.00%)	0 / 14 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural fibrosis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 14 (7.14%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 58 (1.72%)	0 / 14 (0.00%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 58 (1.72%)	0 / 14 (0.00%)	3 / 61 (4.92%)
occurrences causally related to treatment / all	0 / 1	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	2 / 3
Psychiatric disorders			
Disorientation			
subjects affected / exposed	0 / 58 (0.00%)	0 / 14 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
X-ray with contrast upper gastrointestinal tract abnormal			
subjects affected / exposed	0 / 58 (0.00%)	0 / 14 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	1 / 58 (1.72%)	0 / 14 (0.00%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			

subjects affected / exposed	1 / 58 (1.72%)	0 / 14 (0.00%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laceration			
subjects affected / exposed	1 / 58 (1.72%)	0 / 14 (0.00%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			
subjects affected / exposed	0 / 58 (0.00%)	1 / 14 (7.14%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar vertebral fracture			
subjects affected / exposed	1 / 58 (1.72%)	0 / 14 (0.00%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound complication			
subjects affected / exposed	1 / 58 (1.72%)	0 / 14 (0.00%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	0 / 58 (0.00%)	1 / 14 (7.14%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 58 (0.00%)	0 / 14 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	1 / 58 (1.72%)	0 / 14 (0.00%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive encephalopathy			

subjects affected / exposed	0 / 58 (0.00%)	0 / 14 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	1 / 58 (1.72%)	0 / 14 (0.00%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 58 (0.00%)	0 / 14 (0.00%)	2 / 61 (3.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 58 (3.45%)	0 / 14 (0.00%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 58 (1.72%)	0 / 14 (0.00%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	1 / 58 (1.72%)	0 / 14 (0.00%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 58 (0.00%)	0 / 14 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 58 (1.72%)	0 / 14 (0.00%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 58 (1.72%)	0 / 14 (0.00%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pathological fracture			
subjects affected / exposed	1 / 58 (1.72%)	0 / 14 (0.00%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Anal abscess			
subjects affected / exposed	0 / 58 (0.00%)	0 / 14 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 58 (0.00%)	0 / 14 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	2 / 58 (3.45%)	0 / 14 (0.00%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lobar pneumonia			
subjects affected / exposed	0 / 58 (0.00%)	0 / 14 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Necrotising fasciitis			
subjects affected / exposed	1 / 58 (1.72%)	0 / 14 (0.00%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Perirectal abscess			
subjects affected / exposed	0 / 58 (0.00%)	0 / 14 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pneumonia			
subjects affected / exposed	2 / 58 (3.45%)	0 / 14 (0.00%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	2 / 58 (3.45%)	0 / 14 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 58 (1.72%)	0 / 14 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Prior sunitinib	Prior cytokines	Other prior anti VEGF
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 58 (48.28%)	12 / 14 (85.71%)	33 / 61 (54.10%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 58 (3.45%)	1 / 14 (7.14%)	0 / 61 (0.00%)
occurrences (all)	5	1	0
Blood creatinine increased			
subjects affected / exposed	1 / 58 (1.72%)	1 / 14 (7.14%)	1 / 61 (1.64%)
occurrences (all)	1	1	1
Blood pressure increased			
subjects affected / exposed	0 / 58 (0.00%)	1 / 14 (7.14%)	1 / 61 (1.64%)
occurrences (all)	0	1	1
Blood uric acid increased			
subjects affected / exposed	0 / 58 (0.00%)	1 / 14 (7.14%)	1 / 61 (1.64%)
occurrences (all)	0	1	2
Hepatitis B DNA increased			
subjects affected / exposed	0 / 58 (0.00%)	1 / 14 (7.14%)	0 / 61 (0.00%)
occurrences (all)	0	1	0

Lymphocyte count decreased subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	1 / 14 (7.14%) 1	0 / 61 (0.00%) 0
Weight decreased subjects affected / exposed occurrences (all)	2 / 58 (3.45%) 2	1 / 14 (7.14%) 1	0 / 61 (0.00%) 0
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	2 / 58 (3.45%) 2	1 / 14 (7.14%) 1	1 / 61 (1.64%) 1
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	8 / 58 (13.79%) 9	4 / 14 (28.57%) 6	8 / 61 (13.11%) 8
Iron deficiency anaemia subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	1 / 14 (7.14%) 1	1 / 61 (1.64%) 1
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	1 / 14 (7.14%) 3	2 / 61 (3.28%) 2
General physical health deterioration subjects affected / exposed occurrences (all)	3 / 58 (5.17%) 3	0 / 14 (0.00%) 0	1 / 61 (1.64%) 1
Pyrexia subjects affected / exposed occurrences (all)	2 / 58 (3.45%) 2	1 / 14 (7.14%) 1	5 / 61 (8.20%) 5
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	5 / 58 (8.62%) 7	0 / 14 (0.00%) 0	1 / 61 (1.64%) 1
Mouth ulceration subjects affected / exposed occurrences (all)	2 / 58 (3.45%) 2	1 / 14 (7.14%) 1	2 / 61 (3.28%) 2
Stomatitis			

subjects affected / exposed occurrences (all)	5 / 58 (8.62%) 6	5 / 14 (35.71%) 5	8 / 61 (13.11%) 9
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 58 (3.45%)	0 / 14 (0.00%)	4 / 61 (6.56%)
occurrences (all)	2	0	4
Oropharyngeal pain			
subjects affected / exposed	0 / 58 (0.00%)	1 / 14 (7.14%)	0 / 61 (0.00%)
occurrences (all)	0	1	0
Pneumonitis			
subjects affected / exposed	1 / 58 (1.72%)	1 / 14 (7.14%)	4 / 61 (6.56%)
occurrences (all)	2	1	4
Pneumothorax			
subjects affected / exposed	0 / 58 (0.00%)	1 / 14 (7.14%)	0 / 61 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	0 / 58 (0.00%)	1 / 14 (7.14%)	0 / 61 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	4 / 58 (6.90%)	0 / 14 (0.00%)	0 / 61 (0.00%)
occurrences (all)	8	0	0
Infections and infestations			
Localised infection			
subjects affected / exposed	0 / 58 (0.00%)	1 / 14 (7.14%)	0 / 61 (0.00%)
occurrences (all)	0	1	0
Tonsillitis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 14 (7.14%)	0 / 61 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	3 / 58 (5.17%)	0 / 14 (0.00%)	1 / 61 (1.64%)
occurrences (all)	4	0	1
Metabolism and nutrition disorders			
Diabetes mellitus			

subjects affected / exposed	0 / 58 (0.00%)	1 / 14 (7.14%)	0 / 61 (0.00%)
occurrences (all)	0	1	0
Hypercholesterolaemia			
subjects affected / exposed	3 / 58 (5.17%)	2 / 14 (14.29%)	3 / 61 (4.92%)
occurrences (all)	3	2	3
Hyperglycaemia			
subjects affected / exposed	3 / 58 (5.17%)	1 / 14 (7.14%)	5 / 61 (8.20%)
occurrences (all)	3	1	6
Hypertriglyceridaemia			
subjects affected / exposed	3 / 58 (5.17%)	2 / 14 (14.29%)	4 / 61 (6.56%)
occurrences (all)	3	4	5

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 November 2012	A change in the sample size of the study. The prior cytokines therapy cohort no longer required a minimum number of patients to be treated with bevacizumab. This change was based upon evidence that there was a decrease in the use of cytokines for advanced mRCC since finalization of the original protocol. An update to hepatitis guidelines to align with current standard Afinitor®/RAD template language which was based upon the update to the everolimus core data sheet. This change provide criteria for identification of patients at risk for hepatitis B and C and also provided guidance to Investigators on prophylactic treatment and monitoring for reactivation of disease; An update to pregnancy language to align with current standard Afinitor®/RAD template language which was based upon the update to the everolimus core data sheet. This extended the duration of use of adequate contraception after the last dose of drug for up to 8 weeks.
02 August 2013	•A change in the sample size section of the protocol. The other prior anti-VEGF therapy cohorts no longer required a minimum number of patients to be treated with bevacizumab. This change was based upon evidence that there was a decrease in the use of bevacizumab as first-line treatment. An update to pregnancy language to align with the update to the Investigator's Brochure edition 11 erratum.
18 May 2014	A clarification of the end of study and last patient last visit date. The addition of treatment options for patients still benefiting from everolimus treatment at the end of study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com/CtrdWeb/home.novfor> for complete trial results.

Notes: