Clinical trial results:
A multi-centric, open-label, phase II study investigating the combination of Afinitor with paclitaxel and carboplatin in first line treatment of patients with advanced (stage IV) Large Cell Lung Cancer with neuroendocrine differentiation (LC-NEC)

Summary

EudraCT number	2010-022273-34
Trial protocol	DE
Global end of trial date	13 March 2015

Results information

Result version number	v1 (current)
This version publication date	03 July 2016
First version publication date	03 July 2016

Trial information

Trial identification

Sponsor protocol code	CRAD001KDE37

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Novartis Pharm 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	13 March 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 March 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary endpoint was the proportion of subjects progression-free at Month 3 as assessed by the central reviewer according to RECIST (Version 1.1).

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	28 April 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	Germany: 49
Worldwide total number of subjects	49
EEA total number of subjects	49

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)	29
From 65 to 84 years	20
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This was an open-label, single arm study.

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 plus paclitaxel/carboplatin

Arm description:

Participants received RAD001 5 mg orally once daily in combination with carboplatin and paclitaxel for a maximum 4 cycles or until discontinuation.

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:

5 mg by mouth once daily

Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Area under the curve (AUC) 5 iv every 21 days for 4 cycles

Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

175 mg/m2 intravenously (iv) every 21 days for 4 cycles

Number of subjects in period 1	RAD001 plus paclitaxel/carboplatin
Started	49
Completed	0
Not completed	49
Adverse event, serious fatal	6
Abnormal laboratory value(s)	1
Consent withdrawn by subject	5
Disease progression	25
Adverse event, non-fatal	7
New cancer therapy	5

Baseline characteristics

Reporting groups	
Reporting group title	RAD001 plus paclitaxel/carboplatin
Reporting group description:	
Participants received RAD001 5 mg orally once daily in combination with carboplatin and paclitaxel for a maximum 4 cycles or until discontinuation.	

Reporting group values	RAD001 plus paclitaxel/carboplatin	Total	
Number of subjects	49	49	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	29	29	
From 65-84 years	20	20	
85 years and over	0	0	
Age Continuous | Units: Years			
arithmetic mean	62		
standard deviation	± 8.9	-	
Gender, Male/Female Units: Participants			
Female	14	14	
Male	35	35	

End points

End points reporting groups

Reporting group title	RAD001 plus paclitaxel/carboplatin

Reporting group description:

Participants received RAD001 5 mg orally once daily in combination with carboplatin and paclitaxel for a maximum 4 cycles or until discontinuation.

Primary: Percentage of participants progression-free (PF)

End point title	Percentage of participants progression-free (PF)[1]

End point description:

Tumors were assessed according to Response Evaluation Criteria in Solid tumors (RECIST) to determine PF status. Complete response (CR): disappearance of all lesions (i.e. all evidence of disease, not just the target lesions) determined by 2 observations not less than 4 weeks apart; Partial response (PR): > 30% decrease in the sum of longest diameters of target lesions compared to baseline, with response or stable disease observed in non-target lesions, and no new lesions; Stable disease (SD): neither sufficient shrinkage to qualify for response or sufficient increase to qualify for progressive disease in target lesions, with response or stable disease observed in non-target lesions, and no new lesions; Progressive disease (PD): > 20% increase in the sum of longest diameters of target lesions compared to smallest sum longest diameter recorded. In addition, the sum must also demonstrate an absolute increase of at least 5mm. No statistical analysis was planned for this outcome measure.

End point type	Primary

End point timeframe:

3 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 this primary end point.

End point values	RAD001 plus paclitaxel/carboplatin			
Subject group type	Reporting group			
Number of subjects analysed	49			
Units: Percentage of participants				
number (not applicable)	49			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants progression-free

End point title	Percentage of participants progression-free

End point description:

Tumors were assessed according to Response Evaluation Criteria in Solid tumors (RECIST) to determine progression-free status. Complete response (CR) is disappearance of all lesions (i.e. all evidence of disease, not just the target lesions) determined by 2 observations not less than 4 weeks apart; Partial response (PR) is > 30% decrease in the sum of longest diameters of target lesions compared to baseline, with response or stable disease observed in non-target lesions, and no new lesions; Stable disease (SD) is neither sufficient shrinkage to qualify for response or sufficient increase to qualify for progressive disease in target lesions, with response or stable disease observed in non-target lesions,

and no new lesions; and Progressive disease (PD is: > 20% increase in the sum of longest diameters of target lesions compared to smallest sum longest diameter recorded. In addition, the sum must also demonstrate an absolute increase of at least 5mm.

End point type	Secondary

End point timeframe:

6 months

End point values	RAD001 plus paclitaxel/carboplatin			
Subject group type	Reporting group			
Number of subjects analysed	49			
Units: Percentage of participants				
number (not applicable)	8.2			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with Overall Response Rate (ORR)

End point title	Percentage of participants with Overall Response Rate (ORR)

End point description:

ORR was defined as is the proportion of participants with a best overall response of CR or PR. CR is disappearance of all lesions (i.e. all evidence of disease, not just the target lesions) determined by 2 observations not less than 4 weeks apart; Partial response. PR is > 30% decrease in the sum of longest diameters of target lesions compared to baseline, with response or stable disease observed in non-target lesions, and no new lesions.

End point type	Secondary

End point timeframe:

3 months

End point values	RAD001 plus paclitaxel/carboplatin			
Subject group type	Reporting group			
Number of subjects analysed	49			
Units: Percentage of participants				
number (not applicable)	44.9			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with Disease Control Rate (DCR)

End point title	Percentage of participants with Disease Control Rate (DCR)

End point description:

DCR was defined as is the percentage of participants with a best overall response of CR or PR or SD. Complete response (CR) is disappearance of all lesions (i.e. all evidence of disease, not just the target lesions) determined by 2 observations not less than 4 weeks apart; Partial response (PR) is > 30% decrease in the sum of longest diameters of target lesions compared to baseline, with response or stable disease observed in non-target lesions, and no new lesions; Stable disease (SD) is neither sufficient shrinkage to qualify for response or sufficient increase to qualify for progressive disease in target lesions, with response or stable disease observed in non-target lesions, and no new lesions; and Progressive disease (PD is: > 20% increase in the sum of longest diameters of target lesions compared to smallest sum longest diameter recorded. In addition, the sum must also demonstrate an absolute increase of at least 5mm.

End point type	Secondary

End point timeframe:

3 months

End point values	RAD001 plus paclitaxel/carboplatin			
Subject group type	Reporting group			
Number of subjects analysed	49			
Units: Percentage of participants				
number (not applicable)	73.5			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

PFS was defined as the time from the date of start of treatment to date of event defined as the first documented progression or death due to any cause.

End point type	Secondary

End point timeframe:

6 months

End point values	RAD001 plus paclitaxel/carboplatin			
Subject group type	Reporting group			
Number of subjects analysed	49			
Units: Days				
median (confidence interval 95%)	132 (97 to 181)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

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

End point type	Secondary

End point timeframe:

12 months

End point values	RAD001 plus paclitaxel/carboplatin			
Subject group type	Reporting group			
Number of subjects analysed	49			
Units: Days				
median (confidence interval 95%)	298 (207 to 351)			

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

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	RAD001 plus paclitaxel/carboplatin

Reporting group description:

RAD001 plus paclitaxel/carboplatin

Serious adverse events	RAD001 plus paclitaxel/carboplatin		
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 49 (57.14%)		
number of deaths (all causes)	8		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
BENIGN NEOPLASM OF THYROID GLAND			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
BRONCHIAL CARCINOMA			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
MALIGNANT NEOPLASM PROGRESSION			

subjects affected / exposed	1 / 49 (2.04%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
METASTASES TO CENTRAL NERVOUS SYSTEM				
subjects affected / exposed	1 / 49 (2.04%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
PARANEOPLASTIC SYNDROME				
subjects affected / exposed	1 / 49 (2.04%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
FATIGUE				
subjects affected / exposed	1 / 49 (2.04%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
GENERAL PHYSICAL HEALTH DETERIORATION				
subjects affected / exposed	5 / 49 (10.20%)			
occurrences causally related to treatment / all	2 / 5			
deaths causally related to treatment / all	0 / 0			
MULTI-ORGAN FAILURE				
subjects affected / exposed	1 / 49 (2.04%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
PAIN				
subjects affected / exposed	2 / 49 (4.08%)			
occurrences causally related to treatment / all	1 / 6			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
DYSPNOEA				

subjects affected / exposed	5 / 49 (10.20%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 1		
HAEMOPTYSIS			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
PLEURAL EFFUSION			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
PNEUMOTHORAX			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
PULMONARY EMBOLISM			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
RESPIRATORY FAILURE			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Investigations			
C-REACTIVE PROTEIN INCREASED			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
ATRIAL FIBRILLATION			
subjects affected / exposed	2 / 49 (4.08%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			

SCIATICA				
subjects affected / exposed	1 / 49 (2.04%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
VOCAL CORD PARESIS				
subjects affected / exposed	1 / 49 (2.04%)			
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	1 / 49 (2.04%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
FEBRILE NEUTROPENIA				
subjects affected / exposed	1 / 49 (2.04%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
NEUTROPENIA				
subjects affected / exposed	1 / 49 (2.04%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Ear and labyrinth disorders				
VERTIGO				
subjects affected / exposed	1 / 49 (2.04%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
ABDOMINAL PAIN				
subjects affected / exposed	1 / 49 (2.04%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
ABDOMINAL PAIN UPPER				

subjects affected / exposed	2 / 49 (4.08%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
COLITIS				
subjects affected / exposed	1 / 49 (2.04%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
CONSTIPATION				
subjects affected / exposed	2 / 49 (4.08%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
DIARRHOEA				
subjects affected / exposed	1 / 49 (2.04%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
GASTRITIS				
subjects affected / exposed	1 / 49 (2.04%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
GASTROINTESTINAL HAEMORRHAGE				
subjects affected / exposed	1 / 49 (2.04%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
NAUSEA				
subjects affected / exposed	1 / 49 (2.04%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
ACUTE HEPATIC FAILURE				
subjects affected / exposed	1 / 49 (2.04%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
HEPATOMEGALY				

subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
PAIN IN JAW			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
SPINAL PAIN			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
CLOSTRIDIAL INFECTION			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
EMPYEMA			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
EPIDIDYMITIS			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
GASTROENTERITIS			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
INFECTION			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

PNEUMONIA			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 2		
PYOPNEUMOTHORAX			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
SEPSIS			
subjects affected / exposed	2 / 49 (4.08%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	1 / 2		
SINUSITIS			
subjects affected / exposed	1 / 49 (2.04%)		
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 / 49 (4.08%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
HYPONATRAEMIA			
subjects affected / exposed	2 / 49 (4.08%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	RAD001 plus paclitaxel/carboplatin		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	43 / 49 (87.76%)		
Investigations			
WEIGHT DECREASED			

subjects affected / exposed	8 / 49 (16.33%)		
occurrences (all)	8		
WHITE BLOOD CELL COUNT DECREASED			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences (all)	3		
Nervous system disorders			
HEADACHE			
subjects affected / exposed	6 / 49 (12.24%)		
occurrences (all)	6		
HYPOAESTHESIA			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences (all)	5		
PARAESTHESIA			
subjects affected / exposed	7 / 49 (14.29%)		
occurrences (all)	7		
POLYNEUROPATHY			
subjects affected / exposed	9 / 49 (18.37%)		
occurrences (all)	10		
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	14 / 49 (28.57%)		
occurrences (all)	16		
LEUKOPENIA			
subjects affected / exposed	7 / 49 (14.29%)		
occurrences (all)	12		
NEUTROPENIA			
subjects affected / exposed	10 / 49 (20.41%)		
occurrences (all)	19		
THROMBOCYTOPENIA			
subjects affected / exposed	8 / 49 (16.33%)		
occurrences (all)	12		
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	4 / 49 (8.16%)		
occurrences (all)	4		
CHEST PAIN			

subjects affected / exposed	3 / 49 (6.12%)		
occurrences (all)	3		
FATIGUE			
subjects affected / exposed	17 / 49 (34.69%)		
occurrences (all)	23		
GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences (all)	3		
MUCOSAL INFLAMMATION			
subjects affected / exposed	8 / 49 (16.33%)		
occurrences (all)	8		
OEDEMA PERIPHERAL			
subjects affected / exposed	7 / 49 (14.29%)		
occurrences (all)	8		
PAIN			
subjects affected / exposed	6 / 49 (12.24%)		
occurrences (all)	6		
PERIPHERAL SWELLING			
subjects affected / exposed	4 / 49 (8.16%)		
occurrences (all)	5		
PYREXIA			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences (all)	3		
Eye disorders			
VISUAL IMPAIRMENT			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences (all)	3		
Gastrointestinal disorders			
ABDOMINAL PAIN UPPER			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences (all)	4		
CONSTIPATION			
subjects affected / exposed	9 / 49 (18.37%)		
occurrences (all)	11		
DIARRHOEA			

subjects affected / exposed occurrences (all) DYSPHAGIA subjects affected / exposed occurrences (all) NAUSEA subjects affected / exposed occurrences (all) STOMATITIS subjects affected / exposed occurrences (all)	10 / 49 (20.41%) 13 3 / 49 (6.12%) 3 13 / 49 (26.53%) 16 8 / 49 (16.33%) 11		
Respiratory, thoracic and mediastinal disorders COUGH subjects affected / exposed occurrences (all) DYSPHONIA subjects affected / exposed occurrences (all) DYSPNOEA subjects affected / exposed occurrences (all) OROPHARYNGEAL PAIN subjects affected / exposed occurrences (all)	 8 / 49 (16.33%) 9 3 / 49 (6.12%) 3 13 / 49 (26.53%) 14 3 / 49 (6.12%) 4		
Skin and subcutaneous tissue disorders ALOPECIA subjects affected / exposed occurrences (all) NIGHT SWEATS subjects affected / exposed occurrences (all) RASH subjects affected / exposed occurrences (all)	 12 / 49 (24.49%) 12 4 / 49 (8.16%) 4 7 / 49 (14.29%) 7		
Psychiatric disorders			

INSOMNIA subjects affected / exposed occurrences (all) SLEEP DISORDER subjects affected / exposed occurrences (all)	 3 / 49 (6.12%) 4 5 / 49 (10.20%) 5		
Musculoskeletal and connective tissue disorders ARTHRALGIA subjects affected / exposed occurrences (all) GROWING PAINS subjects affected / exposed occurrences (all) PAIN IN EXTREMITY subjects affected / exposed occurrences (all)	 5 / 49 (10.20%) 8 3 / 49 (6.12%) 3 3 / 49 (6.12%) 5		
Infections and infestations INFECTION subjects affected / exposed occurrences (all)	 4 / 49 (8.16%) 4		
Metabolism and nutrition disorders DECREASED APPETITE subjects affected / exposed occurrences (all) HYPOKALAEMIA subjects affected / exposed occurrences (all)	 10 / 49 (20.41%) 12 5 / 49 (10.20%) 5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 July 2013	Amendment 1 was primarily written to increase recruitment by updating the inclusion/exclusion criteria in order to better reflect the actual patient population and to enlarge the patient population eligible to be enrolled in this study. Inclusion criterion 2 was changed in a manner that a histological confirmation of LC-NEC diagnosis for relapsing tumors was not necessarily needed anymore at time of recurrence. The histological diagnosis of LC-NEC was still necessary but could also be done during an earlier stage of disease. The diagnosis of LC-NEC depending on neuroendocrine differentiation was specified by including the requirement of non-small cell cytological characteristics (in order to exclude SCLC). The increased proliferation rate had to be demonstrated in histology by microscopic analysis (>11/10 HPF) and, if available, by the Ki67 proliferation marker (>50%). In the exclusion criteria, some ambiguous wordings were specified, especially for allowed prior chemotherapies and for radiotherapies of brain metastases. In addition, some inconsistencies in the protocol were amended: The allowed infusion time of the carboplatin infusion was now consistently 30 to 60 minutes and Figure 6-1 with the study treatment scheme was corrected accordingly. The description of RAD001 maintenance treatment after completion of combination treatment was shifted in a separate paragraph. An error in Table 6-4 was corrected. A wording in the paragraph “End of treatment” was amended. The allowed window for visit scheduling was clarified to +/- 3 days if not otherwise specified. Minor amendments in the visit evaluation schedule were made. Inconsistencies regarding the assessment of the primary and secondary efficacy parameters were corrected: The efficacy endpoints (with exception of overall survival) were assessed by the central imaging reviewer. In the statistical part of the protocol, the definition of the ITT set was corrected and the handling of the ITT set was clarified.
17 November 2014	Amendment 2 was written for the purpose to terminate the enrollment to the trial. The termination was effective with approval of this protocol amendment by the Institutional Review Board (IRBs)/ Independent Ethics Committee (IECs) and Health Authorities. The reason for the termination was the low recruitment rate. Since the first patient was enrolled in April 2011, altogether only 48 patients (cut-off date 17-Nov-2014) could be recruited at 11 active study sites. Several actions were taken to improve the recruitment rate: implementation of protocol amendment 1 which updated the inclusion/exclusion criteria in order to better reflect the actual patient population and to enlarge the patient population eligible to be enrolled in this study; two investigator meetings including the site pathologists; a separate pathologist board; opening of two additional study sites; advertising for the trial in the internet; and several preliminary publications at scientific meetings. However, as the recruitment rate did not improve noteworthy, it could not be expected that the originally planned number of patients (71 evaluable patients) could be reached in a reasonable time.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported