



## 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:

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**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:

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**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:

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**Population of trial subjects**

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**Subjects enrolled per country**

|                                      |             |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Germany: 49 |
| Worldwide total number of subjects   | 49          |
| EEA total number of subjects         | 49          |

Notes:

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**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/m<sup>2</sup> intravenously (iv) every 21 days for 4 cycles

| <b>Number of subjects in period 1</b> | <b>RAD001 plus<br/>paclitaxel/carboplatin</b> |
|---------------------------------------|---|
| 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<br>paclitaxel/carboplatin | Total |  |
|---|---------------------------------------|-------|--|
| Number of subjects                                    | 49                                    | 49    |  |
| Age categorical<br>Units: Subjects                    |                                       |       |  |
| In utero  | 0                                     | 0     |  |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0                                     | 0     |  |
| Newborns (0-27 days)                                  | 0                                     | 0     |  |
| Infants and toddlers (28 days-23<br>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  <br>Units: Years                      |                                       |       |  |
| arithmetic mean                                       | 62                                    |       |  |
| standard deviation                                    | ± 8.9                                 | -     |  |
| Gender, Male/Female<br>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) <sup>[1]</sup> |
| 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             |           |

|                                   |                                    |  |  |  |
|-----------------------------------|------------------------------------|--|--|--|
| <b>End point values</b>           | 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

|                                   |                                    |  |  |  |
|-----------------------------------|------------------------------------|--|--|--|
| <b>End point values</b>           | 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  |  |

|                                   |                                    |  |  |  |
|-----------------------------------|------------------------------------|--|--|--|
| <b>End point values</b>           | 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  |                                 |

|                                  |                                    |  |  |  |
|----------------------------------|------------------------------------|--|--|--|
| <b>End point values</b>          | 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<br>paclitaxel/carb<br>oplatin |  |  |  |
|----------------------------------|---|--|--|--|
| Subject group type               | Reporting group                           |  |  |  |
| Number of subjects analysed      | 49  |  |  |  |
| Units: Days                      |   |  |  |  |
| median (confidence interval 95%) | 298 (207 to<br>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 %

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



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

|  |                  |  |  |
|--|------------------|--|--|
| subjects affected / exposed              | 3 / 49 (6.12%)   |  |  |
| occurrences (all)                        | 3                |  |  |
| FATIGUE                                  |                  |  |  |
| subjects affected / exposed              | 17 / 49 (34.69%) |  |  |
| occurrences (all)                        | 23               |  |  |
| GENERAL PHYSICAL HEALTH<br>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                                |                  |  |  |

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

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