



## Clinical trial results:

### Phase I/II study of Induction Chemotherapy with weekly RAD001, Carboplatine and Paclitaxel in Unresectable or Inoperable Locally Advanced Head and Neck Squamous Cell Carcinoma (HNSCC)

#### Summary

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2008-005702-39  |
| Trial protocol           | FR              |
| Global end of trial date | 31 January 2013 |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 23 July 2016 |
| First version publication date | 23 July 2016 |

#### Trial information

##### Trial identification

|                       |       |
|-----------------------|-------|
| Sponsor protocol code | O08-1 |
|-----------------------|-------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01333085 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | GERCOR  |
| Sponsor organisation address | 151 rue du faubourg Saint Antoine, PARIS, France, 75011   |
| Public contact               | Regulatory affairs, GERCOR, 33 1 40 29 85 00, regulatory.affairs@gercor.com.fr                    |
| Scientific contact           | coordinating investigator, Pr Sandrine FAIVRE, 33 1 40 29 85 00, regulatory.affairs@gercor.com.fr |

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                       | 31 January 2013 |
| Is this the analysis of the primary completion data? | Yes             |
| Primary completion date                              | 31 January 2013 |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 31 January 2013 |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

Phase I:

To determine the safety profile of weekly RAD001 in combination with carboplatin and paclitaxel in chemo-naïve patients with unresectable or inoperable locally advanced HNSCC.

Phase II: To assess anti-tumor activity of the combination in these patients.

Protection of trial subjects:

Premedication

Administration of paclitaxel should be preceded by an anti-allergic premedication with solumedrol 80 mg IV and polaramine 5 mg IV, and an anti-emetic prophylaxis at the discretion of the investigator.

Dose adjustments:

Doses will be reduced for hematological and other adverse events. Dose adjustments are to be made according to the system showing the greatest degree of toxicity. Adverse events will be graded using the NCI CTCAE version 3.0.

Except for nausea and vomiting, dose reductions are definitive. A maximum of 2 dose reductions are allowed. First dose reduction has to be done on RAD001 and the second one on carboplatin and/or paclitaxel. Patients who should experience a third dose reduction must be dropped out of study. Anemia should be treated according to investigator's discretion. No dose reduction is allowed, but erythropoietin use is permitted.

Background therapy: -

Evidence for comparator: -

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 15 October 2009 |
| Long term follow-up planned                               | No              |
| Independent data monitoring committee (IDMC) involvement? | No              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |            |
|--------------------------------------|------------|
| Country: Number of subjects enrolled | France: 50 |
| Worldwide total number of subjects   | 50         |
| EEA total number of subjects         | 50         |

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)                     | 35 |
| From 65 to 84 years                      | 14 |
| 85 years and over                        | 1  |

## Subject disposition

### Recruitment

Recruitment details:

Patient enrollment occurred from 15 October 2009 (first patient was treated in phase I) to 20 November 2012 (last patient enrolled in phase II).

This study was conducted in France in five centers (Hôpital Beaujon - Clichy; Hôpital St Joseph, Institut Curie - Paris; Centre Léon Bérard Lyon; Institut Claudius Regaud -Toulouse)

### Pre-assignment

Screening details:

Patient with inoperable Locally Advanced Head and Neck Squamous cell carcinoma.

Phase I (permitted to identify the recommended dose level): 7 patients were enrolled: 4 at dose level 1 (RAD001 30mg) and 3 at dose level 2 (RAD001 50mg).

Phase II: 43 patients were enrolled at dose RAD001 50mg.

### Period 1

|                              |   |
|------------------------------|---|
| Period 1 title               | Paclitaxel - Carboplatin - RAD001 50mg (overall period) |
| Is this the baseline period? | Yes   |
| Allocation method            | Not applicable  |
| Blinding used                | Not blinded   |

### Arms

|           |  |
|-----------|--|
| Arm title | Paclitaxel - Carboplatin - RAD001 50mg |
|-----------|--|

Arm description:

Patients received in first-line 9 weekly cycles of RAD001 (50mg) in combination with carboplatin (AUC2) and paclitaxel (60mg/m<sup>2</sup>).

Recommended dose was RAD001 50mg

|  |                       |
|--|-----------------------|
| Arm type                               | Experimental          |
| 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:

Paclitaxel: 60mg/m<sup>2</sup> IV in 1 hour

Before infusion of paclitaxel at D1, D8, D15 a premedication was recommended with one injection of 5 mg polaramine.

|  |                       |
|--|-----------------------|
| Investigational medicinal product name | Carboplatin AUC2      |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

Carboplatin AUC2 in 1 hour

Dose of carboplatin is calculated according to creatinine clearance estimated by Calvert formula and area under curve (AUC).

|  |            |
|--|------------|
| Investigational medicinal product name | RAD001     |
| Investigational medicinal product code |            |
| Other name                             | Everolimus |
| Pharmaceutical forms                   | Tablet     |
| Routes of administration               | Oral use   |

Dosage and administration details:

RAD001 is presented as 10mg tablets. It was orally administered weekly at a dose of 50mg. It was swallowed 1 hour before or 2 hours after lunch with a glass of water.

| <b>Number of subjects in period 1<sup>[1]</sup></b> | <b>Paclitaxel - Carboplatin - RAD001 50mg</b> |
|---|---|
| Started   | 46  |
| Completed   | 41  |
| Not completed                                       | 5   |
| Physician decision                                  | 1   |
| Intercurrent medical event                          | 1   |
| Death (related to cancer)                           | 1   |
| Adverse event, non-fatal                            | 1   |
| Patient choice                                      | 1   |

---

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 50 patients were included in phase I and phase II.

4 patients treated at dose level RAD001 30mg and 3 patients at dose level RAD001 50mg, permitted to identify the recommended dose level (RAD001 50mg)

46 patients treated at the dose level recommended (3 patients phase I and 43 patients phase II) were evaluated (overall period)

## Baseline characteristics

### Reporting groups

|                       |  |
|-----------------------|--|
| Reporting group title | Paclitaxel - Carboplatin - RAD001 50mg |
|-----------------------|--|

Reporting group description:

Analysis of the data's, including the patients treated at recommended dose of RAD001 (50mg/week). (3 patients in phase I and 43 patients in phase II).

| Reporting group values                             | Paclitaxel - Carboplatin - RAD001 50mg | Total |  |
|--|--|-------|--|
| Number of subjects                                 | 46                                     | 46    |  |
| 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)                               | 31                                     | 31    |  |
| From 65-84 years                                   | 14                                     | 14    |  |
| 85 years and over                                  | 1                                      | 1     |  |
| Age continuous                                     |  |       |  |
| Units: years                                       |  |       |  |
| median   | 0                                      |       |  |
| standard deviation                                 | ± 0                                    | -     |  |
| Gender categorical                                 |  |       |  |
| Units: Subjects                                    |  |       |  |
| Female   | 9                                      | 9     |  |
| Male   | 37                                     | 37    |  |
| T-stage  |  |       |  |
| Units: Subjects                                    |  |       |  |
| T1   | 2                                      | 2     |  |
| T2   | 6                                      | 6     |  |
| T3   | 2                                      | 2     |  |
| T4a  | 31                                     | 31    |  |
| T4b  | 4                                      | 4     |  |
| Tx   | 1                                      | 1     |  |
| Missing  | 0                                      | 0     |  |
| N-stage  |  |       |  |
| Units: Subjects                                    |  |       |  |
| N1   | 6                                      | 6     |  |
| N2a  | 3                                      | 3     |  |
| N2b  | 5                                      | 5     |  |
| N2c  | 14                                     | 14    |  |
| N3   | 13                                     | 13    |  |
| Nx   | 4                                      | 4     |  |
| Missing  | 1                                      | 1     |  |

|                           |    |    |  |
|---------------------------|----|----|--|
| Stade                     |    |    |  |
| Units: Subjects           |    |    |  |
| IVa                       | 30 | 30 |  |
| IVb                       | 16 | 16 |  |
| Missing                   | 0  | 0  |  |
| Grade                     |    |    |  |
| Units: Subjects           |    |    |  |
| Well                      | 16 | 16 |  |
| Moderately                | 18 | 18 |  |
| Poorly                    | 7  | 7  |  |
| Not evaluable             | 4  | 4  |  |
| Missing                   | 1  | 1  |  |
| Side                      |    |    |  |
| Units: Subjects           |    |    |  |
| Left                      | 23 | 23 |  |
| Right                     | 17 | 17 |  |
| Both                      | 6  | 6  |  |
| Missing                   | 0  | 0  |  |
| Node                      |    |    |  |
| Units: Subjects           |    |    |  |
| Yes                       | 40 | 40 |  |
| No                        | 6  | 6  |  |
| Missing                   | 0  | 0  |  |
| Tumor Site                |    |    |  |
| Units: Subjects           |    |    |  |
| Oral cavity               | 13 | 13 |  |
| Hypopharynx               | 5  | 5  |  |
| Larynx                    | 4  | 4  |  |
| Oropharynx                | 24 | 24 |  |
| Missing                   | 0  | 0  |  |
| ECOG - Performance status |    |    |  |
| Units: Subjects           |    |    |  |
| ECOG - PS=0               | 22 | 22 |  |
| ECOG - PS=1               | 18 | 18 |  |
| ECOG - PS=2               | 6  | 6  |  |
| Missing                   | 0  | 0  |  |

## End points

### End points reporting groups

|                       |  |
|-----------------------|--|
| Reporting group title | Paclitaxel - Carboplatin - RAD001 50mg |
|-----------------------|--|

Reporting group description:

Patients received in first-line 9 weekly cycles of RAD001 (50mg) in combination with carboplatin (AUC2) and paclitaxel (60mg/m<sup>2</sup>).

Recommended dose was RAD001 50mg

|                            |                              |
|----------------------------|------------------------------|
| Subject analysis set title | Clinical Toxicity, all Grade |
|----------------------------|------------------------------|

|                           |               |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

The adverse events were assessed using the terminology Criteria for adverse Event (CTCAE) version 3.0. Clinical toxicity at the recommended dose (RAD001, 50mg)

|                            |                              |
|----------------------------|------------------------------|
| Subject analysis set title | Clinical Toxicity, Grade 1-2 |
|----------------------------|------------------------------|

|                           |               |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

The adverse events were assessed using the terminology Criteria for adverse Event (CTCAE) version 3.0. Clinical toxicity at the recommended dose (RAD001, 50mg)

|                            |                              |
|----------------------------|------------------------------|
| Subject analysis set title | Clinical Toxicity, Grade 3-4 |
|----------------------------|------------------------------|

|                           |               |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

The adverse events were assessed using the terminology Criteria for adverse Event (CTCAE) version 3.0. Clinical toxicity at the recommended dose (RAD001, 50mg)

|                            |                                |
|----------------------------|--------------------------------|
| Subject analysis set title | Biological Toxicity, All Grade |
|----------------------------|--------------------------------|

|                           |               |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

The adverse events were assessed using the terminology Criteria for adverse Event (CTCAE) version 3.0. At recommended dose (RAD001, 50mg)

|                            |                                |
|----------------------------|--------------------------------|
| Subject analysis set title | Biological Toxicity, Grade 0-1 |
|----------------------------|--------------------------------|

|                           |               |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

The adverse events were assessed using the terminology Criteria for adverse Event (CTCAE) version 3.0. At the recommended dose (RAD001, 50mg)

|                            |                                |
|----------------------------|--------------------------------|
| Subject analysis set title | Biological Toxicity, grade 3-4 |
|----------------------------|--------------------------------|

|                           |               |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

The adverse events were assessed using the terminology Criteria for adverse Event (CTCAE) version 3.0. At the recommended dose RAD001, 50mg

### Primary: Objective Response Rate

|                 |  |
|-----------------|--|
| End point title | Objective Response Rate <sup>[1]</sup> |
|-----------------|--|

End point description:

All eligible patients will be included in the response rate calculation. Objective response rate was according to RECIST criteria.

The subset that will be assigned a response category (CR, PR, SD or PD) are all patients who have received at least one treatment and have their disease re-evaluated.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Evaluation at 11 weeks after first administration.

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: Results of phase II trial will be given as response rates with 95% confidence intervals.



|                             |  |  |  |  |
|-----------------------------|--|--|--|--|
| <b>End point values</b>     | Paclitaxel -<br>Carboplatin -<br>RAD001 50mg |  |  |  |
| Subject group type          | Reporting group                              |  |  |  |
| Number of subjects analysed | 41 <sup>[2]</sup>                            |  |  |  |
| Units: subjects             |  |  |  |  |
| Complete response (CR)      | 1  |  |  |  |
| Partial response (PR)       | 30   |  |  |  |
| Stable disease (SD)         | 9  |  |  |  |
| Progressive disease         | 1  |  |  |  |

Notes:

[2] - 5 patients were not included in efficacy analysis, being not evaluable for tumor response.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Clinical Adverse Event at RAD001 50mg

|   |                                       |
|---|---------------------------------------|
| End point title   | Clinical Adverse Event at RAD001 50mg |
| End point description:  |                                       |
| All patients will be evaluable for toxicity from the time of their first treatment with RAD001, carboplatin and paclitaxel. Safety evaluations were conducted at least weekly until 2 weeks after the end of therapy and included assessments of laboratory parameters and clinical adverse reactions. Clinical adverse events were graded according to the NCI-CTCAE grading system version 3.0. |                                       |
| End point type  | Secondary                             |
| End point timeframe:  |                                       |
| From inclusion to 14 days after radiation therapy completion  |                                       |

| <b>End point values</b>     | Clinical<br>Toxicity, all<br>Grade | Clinical<br>Toxicity, Grade<br>1-2 | Clinical Toxicity,<br>Grade 3-4 |  |
|-----------------------------|------------------------------------|------------------------------------|---------------------------------|--|
| Subject group type          | Subject analysis set               | Subject analysis set               | Subject analysis set            |  |
| Number of subjects analysed | 46                                 | 46                                 | 46                              |  |
| Units: subject              |                                    |                                    |                                 |  |
| Nausea                      | 16                                 | 16                                 | 0                               |  |
| Vomiting                    | 9                                  | 9                                  | 0                               |  |
| Mucositis                   | 13                                 | 13                                 | 0                               |  |
| Constipation                | 11                                 | 11                                 | 0                               |  |
| Alopecia                    | 14                                 | 14                                 | 0                               |  |
| Oedema                      | 2                                  | 2                                  | 0                               |  |
| Asthenia                    | 31                                 | 27                                 | 4                               |  |
| Neuropathy                  | 3                                  | 3                                  | 0                               |  |
| Hand foot syndrome          | 2                                  | 2                                  | 0                               |  |
| Rash                        | 12                                 | 11                                 | 1                               |  |
| Acnea                       | 5                                  | 5                                  | 0                               |  |
| Cough                       | 6                                  | 6                                  | 0                               |  |
| Dyspnea                     | 9                                  | 8                                  | 1                               |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Biological Adverse Events at RAD001 50mg

|                 |  |
|-----------------|--|
| End point title | Biological Adverse Events at RAD001 50mg |
|-----------------|--|

End point description:

All patients will be evaluable for toxicity from the time of their first treatment with RAD001, carboplatin and paclitaxel. Safety evaluations were conducted at least weekly until 2 weeks after the end of therapy and included assessments of laboratory parameters and clinical adverse reactions. Clinical adverse events were graded according to the NCI-CTCAE grading system version 3.0.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From the randomisation to 14 days after radiation therapy completion

| End point values            | Biological Toxicity, All Grade | Biological Toxicity, Grade 0-1 | Biological Toxicity, grade 3-4 |  |
|-----------------------------|--------------------------------|--------------------------------|--------------------------------|--|
| Subject group type          | Subject analysis set           | Subject analysis set           | Subject analysis set           |  |
| Number of subjects analysed | 46                             | 46                             | 46                             |  |
| Units: Subject              |                                |                                |                                |  |
| Leucopenia                  | 39                             | 26                             | 13                             |  |
| Neutropenia                 | 40                             | 16                             | 24                             |  |
| Anemia                      | 43                             | 35                             | 8                              |  |
| Thrombocytopenia            | 37                             | 31                             | 6                              |  |
| Hyperglycemia               | 38                             | 36                             | 2                              |  |
| Hypercholesterolemia        | 27                             | 27                             | 0                              |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Effect of CAPRA study in the expression of biomarkers (Ki67 and p-S6K)

|                 |  |
|-----------------|--|
| End point title | Effect of CAPRA study in the expression of biomarkers (Ki67 and p-S6K) |
|-----------------|--|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Biopsy specimens obtained before treatment (baseline) and post treatment (Post-CAPRA).

|                             |  |  |  |  |
|-----------------------------|--|--|--|--|
| <b>End point values</b>     | Paclitaxel -<br>Carboplatin -<br>RAD001 50mg |  |  |  |
| Subject group type          | Reporting group                              |  |  |  |
| Number of subjects analysed | 46   |  |  |  |
| Units: subject              | 46   |  |  |  |

|                                   |  |
|-----------------------------------|--|
| <b>Attachments (see zip file)</b> | CAPRA biomarkers in biopsies results.pdf |
|-----------------------------------|--|

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the first dose taken to 14 days after radiation therapy completion

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 15.1 |
|--------------------|------|

### Reporting groups

|                       |   |
|-----------------------|---|
| Reporting group title | Paclitaxel - carboplatin- RAD001 (50mg) |
|-----------------------|---|

Reporting group description:

Forty-six patients were evaluable for toxicity.

| Serious adverse events                            | Paclitaxel - carboplatin- RAD001 (50mg)    |  |  |
|---|--|--|--|
| Total subjects affected by serious adverse events |  |  |  |
| subjects affected / exposed                       | 20 / 46 (43.48%)                           |  |  |
| number of deaths (all causes)                     | 1  |  |  |
| number of deaths resulting from adverse events    | 0  |  |  |
| Investigations                                    |  |  |  |
| Platelet count decreased                          | Additional description: grade 4 et grade 2 |  |  |
| subjects affected / exposed                       | 2 / 46 (4.35%)                             |  |  |
| occurrences causally related to treatment / all   | 0 / 0                                      |  |  |
| deaths causally related to treatment / all        | 0 / 0                                      |  |  |
| Neutrophil count decreased                        | Additional description: grade 4            |  |  |
| subjects affected / exposed                       | 1 / 46 (2.17%)                             |  |  |
| occurrences causally related to treatment / all   | 0 / 0                                      |  |  |
| deaths causally related to treatment / all        | 0 / 0                                      |  |  |
| Cardiac disorders                                 |  |  |  |
| Hemorrhage tumoral                                | Additional description: grade 3            |  |  |
| subjects affected / exposed                       | 1 / 46 (2.17%)                             |  |  |
| occurrences causally related to treatment / all   | 0 / 0                                      |  |  |
| deaths causally related to treatment / all        | 0 / 0                                      |  |  |
| Nervous system disorders                          |  |  |  |
| Stroke  | Additional description: grade 3 et grade 2 |  |  |

|  |  |  |  |
|--|--|--|--|
| subjects affected / exposed                          | 2 / 46 (4.35%)   |  |  |
| occurrences causally related to treatment / all      | 0 / 0  |  |  |
| deaths causally related to treatment / all           | 0 / 0  |  |  |
| General disorders and administration site conditions |  |  |  |
| Fever  | Additional description: grade 1                                  |  |  |
| subjects affected / exposed                          | 1 / 46 (2.17%)   |  |  |
| occurrences causally related to treatment / all      | 0 / 0  |  |  |
| deaths causally related to treatment / all           | 0 / 0  |  |  |
| Blood and lymphatic system disorders                 |  |  |  |
| Thrombocytopenia                                     |  |  |  |
| subjects affected / exposed                          | 1 / 46 (2.17%)   |  |  |
| occurrences causally related to treatment / all      | 0 / 0  |  |  |
| deaths causally related to treatment / all           | 0 / 0  |  |  |
| Immune system disorders                              |  |  |  |
| Edema of the uvula                                   | Additional description: grade 2                                  |  |  |
| subjects affected / exposed                          | 1 / 46 (2.17%)   |  |  |
| occurrences causally related to treatment / all      | 0 / 0  |  |  |
| deaths causally related to treatment / all           | 0 / 0  |  |  |
| Gastrointestinal disorders                           |  |  |  |
| Abdominal pain                                       | Additional description: grade 3                                  |  |  |
| subjects affected / exposed                          | 1 / 46 (2.17%)   |  |  |
| occurrences causally related to treatment / all      | 0 / 0  |  |  |
| deaths causally related to treatment / all           | 0 / 0  |  |  |
| Oral hemorrhage                                      | Additional description: grade 2                                  |  |  |
| subjects affected / exposed                          | 1 / 46 (2.17%)   |  |  |
| occurrences causally related to treatment / all      | 0 / 0  |  |  |
| deaths causally related to treatment / all           | 0 / 0  |  |  |
| Respiratory, thoracic and mediastinal disorders      |  |  |  |
| Respiratory failure                                  | Additional description: grade 5 (death not related to treatment) |  |  |
| subjects affected / exposed                          | 1 / 46 (2.17%)   |  |  |
| occurrences causally related to treatment / all      | 0 / 0  |  |  |
| deaths causally related to treatment / all           | 0 / 0  |  |  |
| Dyspnoea   | Additional description: grade 2                                  |  |  |

|   |  |  |  |
|---|--|--|--|
| subjects affected / exposed                     | 2 / 46 (4.35%)   |  |  |
| occurrences causally related to treatment / all | 0 / 0  |  |  |
| deaths causally related to treatment / all      | 0 / 0  |  |  |
| Pneumonitis                                     | Additional description: grade 2                          |  |  |
| subjects affected / exposed                     | 2 / 46 (4.35%)   |  |  |
| occurrences causally related to treatment / all | 0 / 0  |  |  |
| deaths causally related to treatment / all      | 0 / 0  |  |  |
| Infections and infestations                     |  |  |  |
| Febrile syndrome                                | Additional description: grade 1                          |  |  |
| subjects affected / exposed                     | 1 / 46 (2.17%)   |  |  |
| occurrences causally related to treatment / all | 0 / 0  |  |  |
| deaths causally related to treatment / all      | 0 / 0  |  |  |
| Febrile neutropenia                             | Additional description: grade 3                          |  |  |
| subjects affected / exposed                     | 1 / 46 (2.17%)   |  |  |
| occurrences causally related to treatment / all | 0 / 0  |  |  |
| deaths causally related to treatment / all      | 0 / 0  |  |  |
| Abscess   | Additional description: gastrostomy tube abscess grade 2 |  |  |
| subjects affected / exposed                     | 1 / 46 (2.17%)   |  |  |
| occurrences causally related to treatment / all | 0 / 0  |  |  |
| deaths causally related to treatment / all      | 0 / 0  |  |  |
| Metabolism and nutrition disorders              |  |  |  |
| Hypokalemia                                     | Additional description: grade 4                          |  |  |
| subjects affected / exposed                     | 1 / 46 (2.17%)   |  |  |
| occurrences causally related to treatment / all | 0 / 0  |  |  |
| deaths causally related to treatment / all      | 0 / 0  |  |  |

Frequency threshold for reporting non-serious adverse events: 4 %

|   |   |  |  |
|---|---|--|--|
| <b>Non-serious adverse events</b>                     | Paclitaxel - carboplatin- RAD001 (50mg) |  |  |
| Total subjects affected by non-serious adverse events |   |  |  |
| subjects affected / exposed                           | 46 / 46 (100.00%)                       |  |  |
| Nervous system disorders                              |   |  |  |
| Oedema  |   |  |  |

|  |                  |  |  |
|--|------------------|--|--|
| subjects affected / exposed                          | 2 / 46 (4.35%)   |  |  |
| occurrences (all)                                    | 0                |  |  |
| Neuropathy   |                  |  |  |
| subjects affected / exposed                          | 3 / 46 (6.52%)   |  |  |
| occurrences (all)                                    | 0                |  |  |
| General disorders and administration site conditions |                  |  |  |
| Asthenia   |                  |  |  |
| subjects affected / exposed                          | 31 / 46 (67.39%) |  |  |
| occurrences (all)                                    | 0                |  |  |
| Hand foot syndrome                                   |                  |  |  |
| subjects affected / exposed                          | 2 / 46 (4.35%)   |  |  |
| occurrences (all)                                    | 0                |  |  |
| Blood and lymphatic system disorders                 |                  |  |  |
| Leucopenia   |                  |  |  |
| subjects affected / exposed                          | 39 / 46 (84.78%) |  |  |
| occurrences (all)                                    | 0                |  |  |
| Neutropenia  |                  |  |  |
| subjects affected / exposed                          | 40 / 46 (86.96%) |  |  |
| occurrences (all)                                    | 0                |  |  |
| Anemia   |                  |  |  |
| subjects affected / exposed                          | 43 / 46 (93.48%) |  |  |
| occurrences (all)                                    | 0                |  |  |
| Thrombocytopenia                                     |                  |  |  |
| subjects affected / exposed                          | 37 / 46 (80.43%) |  |  |
| occurrences (all)                                    | 0                |  |  |
| Hyperglycemia  |                  |  |  |
| subjects affected / exposed                          | 38 / 46 (82.61%) |  |  |
| occurrences (all)                                    | 0                |  |  |
| hypercholesterolemia                                 |                  |  |  |
| subjects affected / exposed                          | 27 / 46 (58.70%) |  |  |
| occurrences (all)                                    | 0                |  |  |
| Gastrointestinal disorders                           |                  |  |  |
| Nausea   |                  |  |  |
| subjects affected / exposed                          | 16 / 46 (34.78%) |  |  |
| occurrences (all)                                    | 0                |  |  |
| Vomiting   |                  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 9 / 46 (19.57%)  |  |  |
| occurrences (all)                               | 0                |  |  |
| Mucositis management                            |                  |  |  |
| subjects affected / exposed                     | 13 / 46 (28.26%) |  |  |
| occurrences (all)                               | 0                |  |  |
| Constipation                                    |                  |  |  |
| subjects affected / exposed                     | 11 / 46 (23.91%) |  |  |
| occurrences (all)                               | 0                |  |  |
| Respiratory, thoracic and mediastinal disorders |                  |  |  |
| Cough   |                  |  |  |
| subjects affected / exposed                     | 6 / 46 (13.04%)  |  |  |
| occurrences (all)                               | 0                |  |  |
| Dyspnea   |                  |  |  |
| subjects affected / exposed                     | 9 / 46 (19.57%)  |  |  |
| occurrences (all)                               | 0                |  |  |
| Skin and subcutaneous tissue disorders          |                  |  |  |
| Alopecia  |                  |  |  |
| subjects affected / exposed                     | 14 / 46 (30.43%) |  |  |
| occurrences (all)                               | 0                |  |  |
| Rash  |                  |  |  |
| subjects affected / exposed                     | 12 / 46 (26.09%) |  |  |
| occurrences (all)                               | 0                |  |  |
| Acnea   |                  |  |  |
| subjects affected / exposed                     | 5 / 46 (10.87%)  |  |  |
| occurrences (all)                               | 0                |  |  |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 15 February 2010 | Precision concerning inclusion and exclusion criteria. |
| 14 April 2011    | Prolongation of the trial                              |

Notes:

---

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported