



## Clinical trial results:

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

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

## Summary

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

## Results information

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

## Trial information

### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | CRAD001L2404 |
|-----------------------|--------------|

### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01491672 |
| WHO universal trial number (UTN)   | -           |

Notes:

## Sponsors

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

Notes:

## Paediatric regulatory details

|                                                                      |    |
|----------------------------------------------------------------------|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|                                                      |             |
|------------------------------------------------------|-------------|
| Analysis stage                                       | Final       |
| Date of interim/final analysis                       | 05 May 2015 |
| Is this the analysis of the primary completion data? | Yes         |
| Primary completion date                              | 05 May 2015 |
| Global end of trial reached?                         | Yes         |
| Global end of trial date                             | 05 May 2015 |
| Was the trial ended prematurely?                     | No          |

Notes:

## General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

|                                                           |                  |
|-----------------------------------------------------------|------------------|
| Actual start date of recruitment                          | 30 November 2011 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | No               |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | United States: 16      |
| Country: Number of subjects enrolled | China: 55              |
| Country: Number of subjects enrolled | Bulgaria: 8            |
| Country: Number of subjects enrolled | Brazil: 8              |
| Country: Number of subjects enrolled | Argentina: 6           |
| Country: Number of subjects enrolled | Russian Federation: 41 |
| Worldwide total number of subjects   | 134                    |
| EEA total number of subjects         | 8                      |

Notes:

### Subjects enrolled per age group

|                                           |   |
|-------------------------------------------|---|
| In utero                                  | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days)                      | 0 |

|                                          |     |
|------------------------------------------|-----|
| Infants and toddlers (28 days-23 months) | 0   |
| Children (2-11 years)                    | 0   |
| Adolescents (12-17 years)                | 0   |
| Adults (18-64 years)                     | 105 |
| From 65 to 84 years                      | 29  |
| 85 years and over                        | 0   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

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

### Period 1

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

### Arms

|                              |                 |
|------------------------------|-----------------|
| Are arms mutually exclusive? | Yes             |
| <b>Arm title</b>             | Prior sunitinib |

Arm description:

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

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

Dosage and administration details:

10 mg orally once daily

|                  |                                                       |
|------------------|-------------------------------------------------------|
| <b>Arm title</b> | Other prior vascular endothelial growth factor (VEGF) |
|------------------|-------------------------------------------------------|

Arm description:

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

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

Dosage and administration details:

10 mg orally once daily

|                  |                 |
|------------------|-----------------|
| <b>Arm title</b> | Prior cytokines |
|------------------|-----------------|

Arm description:

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

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

Dosage and administration details:

10 mg orally once daily

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

## Baseline characteristics

### Reporting groups

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

| Reporting group values                             | Prior sunitinib | Other prior vascular endothelial growth factor (VEGF) | Prior cytokines |
|----------------------------------------------------|-----------------|-------------------------------------------------------|-----------------|
| Number of subjects                                 | 58              | 62                                                    | 14              |
| Age categorical<br>Units: Subjects                 |                 |                                                       |                 |
| In utero                                           | 0               | 0                                                     | 0               |
| Preterm newborn infants (gestational age < 37 wks) | 0               | 0                                                     | 0               |
| Newborns (0-27 days)                               | 0               | 0                                                     | 0               |
| Infants and toddlers (28 days-23 months)           | 0               | 0                                                     | 0               |
| Children (2-11 years)                              | 0               | 0                                                     | 0               |
| Adolescents (12-17 years)                          | 0               | 0                                                     | 0               |
| Adults (18-64 years)                               | 47              | 49                                                    | 9               |
| From 65-84 years                                   | 11              | 13                                                    | 5               |
| 85 years and over                                  | 0               | 0                                                     | 0               |
| Age Continuous  <br>Units: Years                   |                 |                                                       |                 |
| arithmetic mean                                    | 56              | 56.5                                                  | 60.3            |
| standard deviation                                 | ± 12.06         | ± 11.14                                               | ± 10.59         |
| Gender, Male/Female<br>Units: Participants         |                 |                                                       |                 |
| Female                                             | 15              | 22                                                    | 6               |
| Male                                               | 43              | 40                                                    | 8               |

| Reporting group values                             | Total |  |  |
|----------------------------------------------------|-------|--|--|
| Number of subjects                                 | 134   |  |  |
| Age categorical<br>Units: Subjects                 |       |  |  |
| In utero                                           | 0     |  |  |
| Preterm newborn infants (gestational age < 37 wks) | 0     |  |  |
| Newborns (0-27 days)                               | 0     |  |  |
| Infants and toddlers (28 days-23 months)           | 0     |  |  |
| Children (2-11 years)                              | 0     |  |  |

|                                                                           |     |  |  |
|---------------------------------------------------------------------------|-----|--|--|
| Adolescents (12-17 years)                                                 | 0   |  |  |
| Adults (18-64 years)                                                      | 105 |  |  |
| From 65-84 years                                                          | 29  |  |  |
| 85 years and over                                                         | 0   |  |  |
| Age Continuous  <br>Units: Years<br>arithmetic mean<br>standard deviation | -   |  |  |
| Gender, Male/Female<br>Units: Participants                                |     |  |  |
| Female                                                                    | 43  |  |  |
| Male                                                                      | 91  |  |  |

## End points

### End points reporting groups

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

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

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

#### Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

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

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

### Statistical analyses

No statistical analyses for this end point

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

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



End point timeframe:

20 months

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

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall survival (OS)

|                 |                       |
|-----------------|-----------------------|
| End point title | Overall survival (OS) |
|-----------------|-----------------------|

End point description:

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

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

End point timeframe:

28 months

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

### Statistical analyses

No statistical analyses for this end point

### Secondary: Clinical Benefit Rate (CBR)

|                 |                             |
|-----------------|-----------------------------|
| End point title | Clinical Benefit Rate (CBR) |
|-----------------|-----------------------------|

End point description:

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

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

End point timeframe:

20 months

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

### Statistical analyses

No statistical analyses for this end point

### Secondary: Objective Response Rate (ORR)

|                 |                               |
|-----------------|-------------------------------|
| End point title | Objective Response Rate (ORR) |
|-----------------|-------------------------------|

End point description:

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

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

End point timeframe:

20 months

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

### Statistical analyses

No statistical analyses for this end point

### Secondary: Duration of Response (DoR)

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

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

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

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

Adverse event reporting additional description:

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

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 18.0   |

### Reporting groups

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | Prior sunitinib |
|-----------------------|-----------------|

Reporting group description:

Prior sunitinib

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | Prior cytokines |
|-----------------------|-----------------|

Reporting group description:

Prior cytokines

|                       |                       |
|-----------------------|-----------------------|
| Reporting group title | Other prior anti VEGF |
|-----------------------|-----------------------|

Reporting group description:

Other prior anti VEGF

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

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

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

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

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



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

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

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

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

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

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

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

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

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

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

Notes: