



## Clinical trial results:

### Phase II single agent sorafenib in the treatment of relapsed oesophageal/gastric adenocarcinoma in platinum pre-treated patients.

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2008-005062-31 |
| Trial protocol           | IE             |
| Global end of trial date | 08 May 2013    |

#### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 19 April 2018 |
| First version publication date | 19 April 2018 |

#### Trial information

##### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | ICORG 06-41 |
|-----------------------|-------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01158287 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Cancer Trials Ireland  |
| Sponsor organisation address | Innovation House, Old Finglas Road, Dublin, Ireland, D11 KXN4        |
| Public contact               | Anna Shevlin, Cancer Trials Ireland,<br>anna.shevlin@cancertrials.ie |
| Scientific contact           | Anna Shevlin, Cancer Trials Ireland,<br>anna.shevlin@cancertrials.ie |

Notes:

#### Paediatric regulatory details

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

Notes:

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**Results analysis stage**

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|  |              |
|--|--------------|
| Analysis stage                                       | Final        |
| Date of interim/final analysis                       | 14 July 2015 |
| Is this the analysis of the primary completion data? | Yes          |
| Primary completion date                              | 08 May 2013  |
| Global end of trial reached?                         | Yes          |
| Global end of trial date                             | 08 May 2013  |
| Was the trial ended prematurely?                     | Yes          |

Notes:

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**General information about the trial**

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Main objective of the trial:

To assess the Disease Control rate after 4 months of treatment for each patient (complete response + partial response + stable disease) rate

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Protection of trial subjects:

This clinical study was designed, implemented, and reported in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice (GCP), with applicable local regulations SI 190 of 2004 as amend and European Directive 2001/20/EC. The study was approved by the HPRA and SJH/AMNCH Research Ethics Committee.

Background therapy:

NA

Evidence for comparator:

NA

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 18 March 2010 |
| Long term follow-up planned                               | No            |
| Independent data monitoring committee (IDMC) involvement? | No            |

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

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|                                      |             |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Ireland: 43 |
| Worldwide total number of subjects   | 43          |
| EEA total number of subjects         | 43          |

Notes:

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**Subjects enrolled per age group**

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|   |   |
|---|---|
| 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)      | 27 |
| From 65 to 84 years       | 16 |
| 85 years and over         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

The first patient was enrolled in Mar 2010, 43 patients were recruited. The last patient was recruited Nov 2012 after which the trial was terminated early.

### Pre-assignment

Screening details:

Relapsed platinum pre-treated patients with oesophageal/gastric adenocarcinoma.

### Period 1

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

### Arms

|           |               |
|-----------|---------------|
| Arm title | Overall Trial |
|-----------|---------------|

Arm description:

Relapsed platinum pre-treated patients with oesophageal/gastric adenocarcinoma.

|  |                    |
|--|--------------------|
| Arm type                               | Experimental       |
| Investigational medicinal product name | Sorafenib          |
| Investigational medicinal product code |                    |
| Other name                             | Nexavar            |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

Sorafenib will be administered orally as a twice daily dosage at 400mg bd as long as the study participant continues to gain clinical benefit and no intolerable toxicity occurs. Patients are to return to the site approximately every 28 days for re-supply of sorafenib therapy.

| Number of subjects in period 1 | Overall Trial |
|--------------------------------|---------------|
| Started                        | 43            |
| Completed                      | 42            |
| Not completed                  | 1             |
| Disease Progression            | 1             |

## Baseline characteristics

### Reporting groups

Reporting group title

Overall Trial

Reporting group description:

Relapsed platinum pre-treated patients with oesophageal/gastric adenocarcinoma.

| Reporting group values                             | Overall Trial | Total |  |
|--|---------------|-------|--|
| Number of subjects                                 | 43            | 43    |  |
| 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)                               | 27            | 27    |  |
| From 65-84 years                                   | 16            | 16    |  |
| 85 years and over                                  | 0             | 0     |  |
| Age continuous                                     |               |       |  |
| Units: years                                       |               |       |  |
| arithmetic mean                                    | 61.3          |       |  |
| standard deviation                                 | ± 10.2        | -     |  |
| Gender categorical                                 |               |       |  |
| Units: Subjects                                    |               |       |  |
| Female   | 7             | 7     |  |
| Male   | 36            | 36    |  |
| Ethnic origin                                      |               |       |  |
| Units: Subjects                                    |               |       |  |
| Caucasian  | 42            | 42    |  |
| Asian  | 1             | 1     |  |
| Tumor Stage  |               |       |  |
| Units: Subjects                                    |               |       |  |
| Locally Advanced/Unresectable                      | 6             | 6     |  |
| Distal Metastatic                                  | 36            | 36    |  |
| Data Missing (patient did not start treatment)     | 1             | 1     |  |
| Time from initial diagnosis to relapse             |               |       |  |
| Units: Days  |               |       |  |
| arithmetic mean                                    | 449.9         |       |  |
| standard deviation                                 | ± 363.1       | -     |  |

## End points

### End points reporting groups

|   |               |
|---|---------------|
| Reporting group title   | Overall Trial |
| Reporting group description:  |               |
| Relapsed platinum pre-treated patients with oesophageal/gastric adenocarcinoma. |               |

### Primary: Disease control status

|  |                                       |
|--|---------------------------------------|
| End point title  | Disease control status <sup>[1]</sup> |
| End point description:   |                                       |
| It is measured according to RECIST criteria every 8 weeks during the study. The primary objective was to assess the disease control rate (CR, PR or SD) after 4 months of treatment. |                                       |
| End point type   | Primary                               |

End point timeframe:

After all patients either received 120 days of treatment or progressed or died before receiving 120 days of treatment.

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: Study terminated early (43/54 patients recruited) after an interim report showed 33 patients had progressed before completing 4 months of treatment. At that point, the primary endpoint, number of patients achieving Disease Control, could not reach 22. Due to limited number of patients completing 4 months of treatment, it was not possible to conduct statistical analysis. Main analysis shows lack of efficacy with only 3/36 patients having stable disease before completing 4 months of treatment.

| End point values                       | Overall Trial   |  |  |  |
|--|-----------------|--|--|--|
| Subject group type                     | Reporting group |  |  |  |
| Number of subjects analysed            | 42              |  |  |  |
| Units: Number of Patients              |                 |  |  |  |
| Complete Response                      | 0               |  |  |  |
| Progression of Disease                 | 3               |  |  |  |
| Stable Disease                         | 3               |  |  |  |
| Did not complete 120 days of treatment | 36              |  |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

April 2010 - February 2015 (4 years and 10 months)

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

### Dictionary used

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

|                    |    |
|--------------------|----|
| Dictionary version | 18 |
|--------------------|----|

### Reporting groups

|                       |               |
|-----------------------|---------------|
| Reporting group title | Overall Trial |
|-----------------------|---------------|

Reporting group description:

Relapsed platinum pre-treated patients with oesophageal/gastric adenocarcinoma.

| Serious adverse events  | Overall Trial    |  |  |
|---|------------------|--|--|
| Total subjects affected by serious adverse events                   |                  |  |  |
| subjects affected / exposed   | 29 / 42 (69.05%) |  |  |
| number of deaths (all causes)                                       | 41               |  |  |
| number of deaths resulting from adverse events                      | 2                |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                  |  |  |
| Brain mets  |                  |  |  |
| subjects affected / exposed   | 1 / 42 (2.38%)   |  |  |
| occurrences causally related to treatment / all                     | 0 / 1            |  |  |
| deaths causally related to treatment / all                          | 0 / 0            |  |  |
| Dermatology squamous cell   |                  |  |  |
| subjects affected / exposed   | 1 / 42 (2.38%)   |  |  |
| occurrences causally related to treatment / all                     | 1 / 1            |  |  |
| deaths causally related to treatment / all                          | 0 / 0            |  |  |
| Vascular disorders  |                  |  |  |
| Postural hypotension  |                  |  |  |
| subjects affected / exposed   | 1 / 42 (2.38%)   |  |  |
| occurrences causally related to treatment / all                     | 0 / 1            |  |  |
| deaths causally related to treatment / all                          | 0 / 0            |  |  |
| General disorders and administration site conditions                |                  |  |  |
| Fatigue   |                  |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 7 / 42 (16.67%) |  |  |
| occurrences causally related to treatment / all | 2 / 7           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pain  |                 |  |  |
| subjects affected / exposed                     | 6 / 42 (14.29%) |  |  |
| occurrences causally related to treatment / all | 0 / 6           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Disease progression                             |                 |  |  |
| subjects affected / exposed                     | 2 / 42 (4.76%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Ankle oedema                                    |                 |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Chest pain                                      |                 |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Death   |                 |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Pyrexia   |                 |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Respiratory, thoracic and mediastinal disorders |                 |  |  |
| Shortness of breath                             |                 |  |  |
| subjects affected / exposed                     | 2 / 42 (4.76%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Dyspnoea  |                 |  |  |



|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 1 / 42 (2.38%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hypoxia   |                |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Breathlessness                                  |                |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Haemoptysis                                     |                |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pleural effusion                                |                |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pneumomediastinum                               |                |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Psychiatric disorders                           |                |  |  |
| Confusion                                       |                |  |  |
| subjects affected / exposed                     | 2 / 42 (4.76%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Depression                                      |                |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Investigations                                  |                |  |  |

|   |                |  |  |
|---|----------------|--|--|
| Weight loss                                     |                |  |  |
| subjects affected / exposed                     | 4 / 42 (9.52%) |  |  |
| occurrences causally related to treatment / all | 0 / 4          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Raised bp                                       |                |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Cardiac disorders                               |                |  |  |
| Atrial fibrillation                             |                |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Nervous system disorders                        |                |  |  |
| Collapse/fainting                               |                |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Intracranial haemorrhage                        |                |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Loss of consciousness                           |                |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Gastrointestinal disorders                      |                |  |  |
| Nausea  |                |  |  |
| subjects affected / exposed                     | 3 / 42 (7.14%) |  |  |
| occurrences causally related to treatment / all | 1 / 4          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Constipation                                    |                |  |  |

|   |                 |  |  |  |
|---|-----------------|--|--|--|
| subjects affected / exposed                     | 2 / 42 (4.76%)  |  |  |  |
| occurrences causally related to treatment / all | 2 / 3           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Abdominal pain                                  |                 |  |  |  |
| subjects affected / exposed                     | 3 / 42 (7.14%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 3           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Vomiting  |                 |  |  |  |
| subjects affected / exposed                     | 6 / 42 (14.29%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 7           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Dysphagia                                       |                 |  |  |  |
| subjects affected / exposed                     | 3 / 42 (7.14%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 3           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Crampy abdominal pain                           |                 |  |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Difficulty swallowing                           |                 |  |  |  |
| subjects affected / exposed                     | 2 / 42 (4.76%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Haematemesis                                    |                 |  |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Abdo. distension                                |                 |  |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Abdominal distension                            |                 |  |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 1 / 42 (2.38%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Dilatation of osepagus                          |                |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Esophagitis                                     |                |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hepatobiliary disorders                         |                |  |  |
| Cholecystitis                                   |                |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Skin and subcutaneous tissue disorders          |                |  |  |
| Skin breakdown                                  |                |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Musculoskeletal and connective tissue disorders |                |  |  |
| Arthralgia                                      |                |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Back pain                                       |                |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Lower back pain                                 |                |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

|   |                |  |  |
|---|----------------|--|--|
| Shoulder pain                                   |                |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Backpain  |                |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Left leg pain                                   |                |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pain in hip                                     |                |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Infections and infestations                     |                |  |  |
| Bilateral pneumonia                             |                |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Respiratory tract infection                     |                |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Sepsis  |                |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Metabolism and nutrition disorders              |                |  |  |
| Anorexia  |                |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

|   |                |  |  |
|---|----------------|--|--|
| Loss of appetite                                |                |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Dehydration                                     |                |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

Frequency threshold for reporting non-serious adverse events: 4.76 %

| <b>Non-serious adverse events</b>                     | Overall Trial     |  |  |
|---|-------------------|--|--|
| Total subjects affected by non-serious adverse events |                   |  |  |
| subjects affected / exposed                           | 42 / 42 (100.00%) |  |  |
| Investigations  |                   |  |  |
| Weight loss   |                   |  |  |
| subjects affected / exposed                           | 10 / 42 (23.81%)  |  |  |
| occurrences (all)                                     | 10                |  |  |
| Decreased haemoglobin                                 |                   |  |  |
| subjects affected / exposed                           | 4 / 42 (9.52%)    |  |  |
| occurrences (all)                                     | 4                 |  |  |
| Elevated ggt  |                   |  |  |
| subjects affected / exposed                           | 2 / 42 (4.76%)    |  |  |
| occurrences (all)                                     | 3                 |  |  |
| Vascular disorders                                    |                   |  |  |
| Hypertension  |                   |  |  |
| subjects affected / exposed                           | 9 / 42 (21.43%)   |  |  |
| occurrences (all)                                     | 11                |  |  |
| General disorders and administration site conditions  |                   |  |  |
| Fatigue   |                   |  |  |
| subjects affected / exposed                           | 24 / 42 (57.14%)  |  |  |
| occurrences (all)                                     | 28                |  |  |
| Pain  |                   |  |  |
| subjects affected / exposed                           | 3 / 42 (7.14%)    |  |  |
| occurrences (all)                                     | 3                 |  |  |
| Mucositis   |                   |  |  |

|                                      |                  |  |  |
|--------------------------------------|------------------|--|--|
| subjects affected / exposed          | 3 / 42 (7.14%)   |  |  |
| occurrences (all)                    | 3                |  |  |
| Bilateral ankle oedema               |                  |  |  |
| subjects affected / exposed          | 2 / 42 (4.76%)   |  |  |
| occurrences (all)                    | 2                |  |  |
| Blood and lymphatic system disorders |                  |  |  |
| Anaemia                              |                  |  |  |
| subjects affected / exposed          | 4 / 42 (9.52%)   |  |  |
| occurrences (all)                    | 4                |  |  |
| Gastrointestinal disorders           |                  |  |  |
| Nausea                               |                  |  |  |
| subjects affected / exposed          | 13 / 42 (30.95%) |  |  |
| occurrences (all)                    | 16               |  |  |
| Constipation                         |                  |  |  |
| subjects affected / exposed          | 10 / 42 (23.81%) |  |  |
| occurrences (all)                    | 14               |  |  |
| Abdominal pain                       |                  |  |  |
| subjects affected / exposed          | 6 / 42 (14.29%)  |  |  |
| occurrences (all)                    | 7                |  |  |
| Vomiting                             |                  |  |  |
| subjects affected / exposed          | 6 / 42 (14.29%)  |  |  |
| occurrences (all)                    | 11               |  |  |
| Diarrhoea                            |                  |  |  |
| subjects affected / exposed          | 6 / 42 (14.29%)  |  |  |
| occurrences (all)                    | 8                |  |  |
| Dysphagia                            |                  |  |  |
| subjects affected / exposed          | 2 / 42 (4.76%)   |  |  |
| occurrences (all)                    | 3                |  |  |
| Diarrhea                             |                  |  |  |
| subjects affected / exposed          | 2 / 42 (4.76%)   |  |  |
| occurrences (all)                    | 4                |  |  |
| Diarrohea                            |                  |  |  |
| subjects affected / exposed          | 2 / 42 (4.76%)   |  |  |
| occurrences (all)                    | 2                |  |  |
| Dry mouth                            |                  |  |  |

|  |  |  |  |
|--|--|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Epigastric pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Sore mouth</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Sore tongue</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>2 / 42 (4.76%)</p> <p>2</p> <p>2 / 42 (4.76%)</p> <p>2</p> <p>2 / 42 (4.76%)</p> <p>2</p> <p>2 / 42 (4.76%)</p> <p>2</p>  |  |  |
| <p>Respiratory, thoracic and mediastinal disorders</p> <p>Cough</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Shortness of breath</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dyspnoea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Hoarseness</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>5 / 42 (11.90%)</p> <p>5</p> <p>2 / 42 (4.76%)</p> <p>2</p> <p>2 / 42 (4.76%)</p> <p>2</p> <p>2 / 42 (4.76%)</p> <p>2</p> |  |  |
| <p>Skin and subcutaneous tissue disorders</p> <p>Rash</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Alopecia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Hand-foot syndrome</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Skin rash</p>   | <p>3 / 42 (7.14%)</p> <p>3</p> <p>2 / 42 (4.76%)</p> <p>2</p> <p>2 / 42 (4.76%)</p> <p>2</p>                                 |  |  |



|  |   |  |  |
|--|---|--|--|
| subjects affected / exposed<br>occurrences (all)   | 2 / 42 (4.76%)<br>2   |  |  |
| Psychiatric disorders<br>Anxiety<br>subjects affected / exposed<br>occurrences (all)   | 2 / 42 (4.76%)<br>2   |  |  |
| Musculoskeletal and connective tissue disorders<br>Back pain<br>subjects affected / exposed<br>occurrences (all)   | 2 / 42 (4.76%)<br>3   |  |  |
| Infections and infestations<br>Chest infection<br>subjects affected / exposed<br>occurrences (all)   | 2 / 42 (4.76%)<br>2   |  |  |
| Metabolism and nutrition disorders<br>Anorexia<br>subjects affected / exposed<br>occurrences (all)<br><br>Anorexia<br>subjects affected / exposed<br>occurrences (all)<br><br>Loss of appetite<br>subjects affected / exposed<br>occurrences (all)<br><br>Reduced appetite<br>subjects affected / exposed<br>occurrences (all)<br><br>Hypoalbuminemia<br>subjects affected / exposed<br>occurrences (all)<br><br>Hypocalcemia<br>subjects affected / exposed<br>occurrences (all)<br><br>Poor appetite<br>subjects affected / exposed<br>occurrences (all) | 3 / 42 (7.14%)<br>3<br><br>3 / 42 (7.14%)<br>3<br><br>2 / 42 (4.76%)<br>3<br><br>3 / 42 (7.14%)<br>4<br><br>2 / 42 (4.76%)<br>2<br><br>2 / 42 (4.76%)<br>3<br><br>2 / 42 (4.76%)<br>2 |  |  |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 10 November 2008 | Protocol Version 2: Regulatory authority requested changes. Changes include revised statements of patient protection, updated Patient Information Leaflet and minor administrative changes.   |
| 12 April 2010    | Protocol Version 3: study synopsis added. Details of a transnational sub-study and updates to prohibited medications added, following a Sorafenib IB update. Dose modification and management of treatment-emergent hypertension section amended. Amendments to patient inclusion criteria, clinical and laboratory evaluations, and table of schedule of study procedures. Additional appendices included. Various administrative changes throughout the protocol. |
| 06 October 2011  | Protocol Version 4: administrative changes and safety updates corresponding to the revised Sorafenib SPC dated 13-Sep-2011.   |

Notes:

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### 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.

Study terminated early after 23-Nov-2012 interim report showed 33 patients had progressed before completing 4 months of treatment. At that point the primary endpoint, number of patients achieving Disease Control could not reach 22 so study closed.

Notes: