



Clinical trial results:

A Randomized, Double-blind, Placebo-controlled Phase-III Study of Adjuvant Regorafenib Versus Placebo for Patients with Stage IV Colorectal Cancer After Curative Treatment of Liver Metastases Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2012-004369-42 |
| Trial protocol | BE ES GB IT DE FR |
| Global end of trial date | 29 August 2016 |

Results information

| | |
|--------------------------------|----------------|
| Result version number | v1 (current) |
| This version publication date | 18 August 2017 |
| First version publication date | 18 August 2017 |

Trial information

Trial identification

| | |
|-----------------------|------------------|
| Sponsor protocol code | BAY73-4506/15983 |
|-----------------------|------------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01939223 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Bayer AG |
| Sponsor organisation address | Kaiser-Wilhelm-Allee , Leverkusen, Germany, D-51368 |
| Public contact | Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com |
| Scientific contact | Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com |

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 | 29 August 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 29 August 2016 |
| Global end of trial reached? | Yes |
| Global end of trial date | 29 August 2016 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

To evaluate and compare the efficacy and safety of regorafenib versus placebo in subjects with colorectal cancer (CRC) after curative resection of liver metastasis and completion of all planned chemotherapy.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent form was read by and explained to all subjects. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 02 December 2013 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------|
| Country: Number of subjects enrolled | Spain: 5 |
| Country: Number of subjects enrolled | France: 1 |
| Country: Number of subjects enrolled | Italy: 6 |
| Country: Number of subjects enrolled | Australia: 2 |
| Country: Number of subjects enrolled | China: 1 |
| Country: Number of subjects enrolled | Israel: 1 |
| Country: Number of subjects enrolled | Japan: 5 |
| Country: Number of subjects enrolled | United States: 4 |
| Worldwide total number of subjects | 25 |
| EEA total number of subjects | 12 |

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) | 18 |
| From 65 to 84 years | 7 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

This multinational study was conducted at 32 study centers that screened 65 subjects across 9 countries, between 02 December 2013 (start of enrollment) and 29 August 2016 (last patient last visit).

Pre-assignment

Screening details:

Overall, 65 subjects were screened, of which 40 were screen failures. The remaining 25 subjects were randomized and assigned to treatment. All 25 subjects received treatment.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Arms

| | |
|------------------------------|--------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Regorafenib 160 mg |

Arm description:

Description: Subjects received regorafenib 160 milligram (mg) (4 * 40 mg tablets) orally once daily on a 3 weeks on / 1 week off dosing schedule.

| | |
|--|---------------|
| Arm type | Experimental |
| Investigational medicinal product name | Regorafenib |
| Investigational medicinal product code | BAY73-4506 |
| Other name | |
| Pharmaceutical forms | Coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received regorafenib 160 milligram (mg) (4 * 40 mg tablets) orally once daily on a 3 weeks on / 1 week off dosing schedule.

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Subjects received placebo matching to regorafenib tablet orally once daily on a 3 weeks on / 1 week off dosing schedule.

| | |
|--|---------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received placebo matching to regorafenib tablet orally once daily on a 3 weeks on / 1 week off dosing schedule.

| Number of subjects in period 1 | Regorafenib 160 mg | Placebo |
|--|--------------------|---------|
| Started | 14 | 11 |
| Participants received treatment | 14 | 11 |
| Completed | 1 | 0 |
| Not completed | 13 | 11 |
| AE not associated with disease recurrence | 1 | 1 |
| Consent withdrawn by subject | 6 | - |
| Disease recurrence (radiological recurrence) | 1 | 3 |
| Study stopped by Sponsor | 5 | 7 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|--------------------|
| Reporting group title | Regorafenib 160 mg |
|-----------------------|--------------------|

Reporting group description:

Description: Subjects received regorafenib 160 milligram (mg) (4 * 40 mg tablets) orally once daily on a 3 weeks on / 1 week off dosing schedule.

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Subjects received placebo matching to regorafenib tablet orally once daily on a 3 weeks on / 1 week off dosing schedule.

| Reporting group values | Regorafenib 160 mg | Placebo | Total |
|---|--------------------|--------------|-------|
| Number of subjects | 14 | 11 | 25 |
| Age categorical Units: Subjects | | | |
| Age continuous Units: years arithmetic mean standard deviation | 59.7 ± 11.22 | 57 ± 9.83 | - |
| Gender categorical Units: Subjects | | | |
| Female | 9 | 5 | 14 |
| Male | 5 | 6 | 11 |

End points

End points reporting groups

| | |
|---|-------------------------|
| Reporting group title | Regorafenib 160 mg |
| Reporting group description: | |
| Description: Subjects received regorafenib 160 milligram (mg) (4 * 40 mg tablets) orally once daily on a 3 weeks on / 1 week off dosing schedule. | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Subjects received placebo matching to regorafenib tablet orally once daily on a 3 weeks on / 1 week off dosing schedule. | |
| Subject analysis set title | Full analysis set (FAS) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Full analysis set (FAS) (N = 25): all subjects who were assigned to treatment. | |

Primary: Disease Free Survival (DFS) as assessed by the investigator

| | |
|--|--|
| End point title | Disease Free Survival (DFS) as assessed by the investigator ^[1] |
| End point description: | |
| Disease free survival was evaluated by CT / MRI scans as assessed by the investigator, which was defined as the time (in days) from date of randomization to date of first observed radiographic disease recurrence (RECIST 1.1 criteria for measurable and non-measurable disease) or death due to any cause, if death occurred before disease recurrence was documented. For subjects without documented disease recurrence or death at the time of analysis, the DFS time was censored at the date of the last evaluable CT / MRI scan. | |
| End point type | Primary |
| End point timeframe: | |
| From date of randomization to date of first observed radiographic disease recurrence (RECIST 1.1 criteria for measurable and non-measurable disease) or death due to any cause, if death occurred before disease recurrence was documented. | |

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: This study was prematurely terminated. Analysis was not performed for this endpoint.

| End point values | Regorafenib 160 mg | Placebo | Full analysis set (FAS) | |
|----------------------------------|--------------------|------------------|-------------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 0 ^[2] | 0 ^[3] | 0 ^[4] | |
| Units: days | | | | |
| median (confidence interval 95%) | (to) | (to) | (to) | |

Notes:

[2] - This study was prematurely terminated. Analysis was not performed for this endpoint.

[3] - This study was prematurely terminated. Analysis was not performed for this endpoint.

[4] - This study was prematurely terminated. Analysis was not performed for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

| | |
|---|-----------------------|
| End point title | Overall survival (OS) |
| End point description: | |
| Overall survival (OS) is defined as the time (days) from randomization to death due to any cause. The | |

OS time for subjects alive at the time of analysis will be censored at their last date known to be alive.

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

End point timeframe:

Subjects who experienced disease recurrence (either during treatment or during Active Follow-up), or otherwise withdrew from the study for any reason other than death, were followed for overall survival unless consent was withdrawn.

| End point values | Regorafenib 160 mg | Placebo | Full analysis set (FAS) | |
|----------------------------------|-----------------------|------------------|----------------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 0 ^[5] | 0 ^[6] | 0 ^[7] | |
| Units: days | | | | |
| median (confidence interval 95%) | (to) | (to) | (to) | |

Notes:

[5] - This study was prematurely terminated. Analysis was not performed for this endpoint.

[6] - This study was prematurely terminated. Analysis was not performed for this endpoint.

[7] - This study was prematurely terminated. Analysis was not performed for this endpoint.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of study treatment until 30 days after the last study drug intake

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 19.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------------------------|
| Reporting group title | Regorafenib 160 mg (BAY73-4506) |
|-----------------------|---------------------------------|

Reporting group description:

Subjects received regorafenib 160 mg (4 *40 mg tablets) orally every day for 3 weeks followed by 1 week off treatment plus BSC (best supportive care).

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Subjects received placebo matched to regorafenib tablets orally every day for 3 weeks followed by 1 week off treatment plus BSC (best supportive care).

| Serious adverse events | Regorafenib 160 mg (BAY73-4506) | Placebo | |
|---|---------------------------------|----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 14 (14.29%) | 0 / 11 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Erythema multiforme | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 11 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Generalised erythema | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 11 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Regorafenib 160 mg (BAY73-4506) | Placebo | |
|---|------------------------------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 13 / 14 (92.86%) | 10 / 11 (90.91%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Hair follicle tumour benign | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 11 (9.09%) | |
| occurrences (all) | 0 | 1 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 7 / 14 (50.00%) | 1 / 11 (9.09%) | |
| occurrences (all) | 29 | 2 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 4 / 14 (28.57%) | 2 / 11 (18.18%) | |
| occurrences (all) | 6 | 2 | |
| Chills | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 11 (9.09%) | |
| occurrences (all) | 0 | 1 | |
| Fatigue | | | |
| subjects affected / exposed | 2 / 14 (14.29%) | 3 / 11 (27.27%) | |
| occurrences (all) | 2 | 3 | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 2 / 11 (18.18%) | |
| occurrences (all) | 0 | 2 | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 11 (9.09%) | |
| occurrences (all) | 0 | 1 | |
| Oedema | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 11 (9.09%) | |
| occurrences (all) | 0 | 1 | |
| Pyrexia | | | |
| subjects affected / exposed | 3 / 14 (21.43%) | 0 / 11 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Immune system disorders | | | |
| Contrast media allergy | | | |

| | | | |
|--|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 1 / 11 (9.09%) 1 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dysphonia | | | |
| subjects affected / exposed | 5 / 14 (35.71%) | 1 / 11 (9.09%) | |
| occurrences (all) | 5 | 1 | |
| Nasal congestion | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 11 (9.09%) | |
| occurrences (all) | 0 | 1 | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 11 (9.09%) | |
| occurrences (all) | 0 | 1 | |
| Productive cough | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 11 (9.09%) | |
| occurrences (all) | 0 | 1 | |
| Rhinitis atrophic | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 11 (9.09%) | |
| occurrences (all) | 0 | 1 | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 11 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 2 / 14 (14.29%) | 1 / 11 (9.09%) | |
| occurrences (all) | 6 | 2 | |
| Amylase increased | | | |
| subjects affected / exposed | 2 / 14 (14.29%) | 0 / 11 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 4 / 14 (28.57%) | 0 / 11 (0.00%) | |
| occurrences (all) | 10 | 0 | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 11 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Blood bilirubin increased | | | |

| | | |
|--|-----------------|----------------|
| subjects affected / exposed | 5 / 14 (35.71%) | 0 / 11 (0.00%) |
| occurrences (all) | 7 | 0 |
| Blood bilirubin unconjugated increased | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 11 (0.00%) |
| occurrences (all) | 2 | 0 |
| Blood creatinine decreased | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 1 |
| Blood lactate dehydrogenase increased | | |
| subjects affected / exposed | 3 / 14 (21.43%) | 0 / 11 (0.00%) |
| occurrences (all) | 3 | 0 |
| Gamma-glutamyltransferase increased | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 1 / 11 (9.09%) |
| occurrences (all) | 2 | 1 |
| Lipase increased | | |
| subjects affected / exposed | 4 / 14 (28.57%) | 1 / 11 (9.09%) |
| occurrences (all) | 7 | 4 |
| Lymphocyte count decreased | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 11 (0.00%) |
| occurrences (all) | 2 | 0 |
| Neutrophil count decreased | | |
| subjects affected / exposed | 2 / 14 (14.29%) | 0 / 11 (0.00%) |
| occurrences (all) | 3 | 0 |
| Neutrophil count increased | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 |
| Platelet count decreased | | |
| subjects affected / exposed | 4 / 14 (28.57%) | 0 / 11 (0.00%) |
| occurrences (all) | 9 | 0 |
| Weight decreased | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 |
| Weight increased | | |

| | | | |
|--|----------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 1 / 11 (9.09%) 2 | |
| White blood cell count decreased subjects affected / exposed occurrences (all) | 3 / 14 (21.43%) 5 | 0 / 11 (0.00%) 0 | |
| White blood cell count increased subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 1 | 0 / 11 (0.00%) 0 | |
| White blood cells urine positive subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 1 / 11 (9.09%) 1 | |
| Injury, poisoning and procedural complications Humerus fracture subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 1 / 11 (9.09%) 1 | |
| Thermal burn subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 1 | 0 / 11 (0.00%) 0 | |
| Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 1 / 11 (9.09%) 1 | |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 1 / 11 (9.09%) 1 | |
| Headache subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 2 | 1 / 11 (9.09%) 1 | |
| Neuropathy peripheral subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 1 / 11 (9.09%) 1 | |
| Peripheral sensory neuropathy subjects affected / exposed occurrences (all) | 2 / 14 (14.29%) 3 | 0 / 11 (0.00%) 0 | |
| Blood and lymphatic system disorders | | | |

| | | | |
|-----------------------------|-----------------|-----------------|--|
| Anaemia | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 11 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 11 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 11 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 1 / 11 (9.09%) | |
| occurrences (all) | 1 | 1 | |
| Anal fistula | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 11 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Cheilitis | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 11 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Constipation | | | |
| subjects affected / exposed | 4 / 14 (28.57%) | 2 / 11 (18.18%) | |
| occurrences (all) | 5 | 2 | |
| Dental caries | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 11 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 3 / 11 (27.27%) | |
| occurrences (all) | 1 | 5 | |
| Flatulence | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 11 (9.09%) | |
| occurrences (all) | 0 | 1 | |
| Gingival pain | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 11 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Nausea | | | |

| | | | |
|--|----------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 1 | 1 / 11 (9.09%) 2 | |
| Stomatitis subjects affected / exposed occurrences (all) | 2 / 14 (14.29%) 2 | 2 / 11 (18.18%) 2 | |
| Toothache subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 1 / 11 (9.09%) 1 | |
| Vomiting subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 1 / 11 (9.09%) 1 | |
| Hepatobiliary disorders Hyperbilirubinaemia subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 4 | 0 / 11 (0.00%) 0 | |
| Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 1 | 0 / 11 (0.00%) 0 | |
| Dermatitis acneiform subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 1 | 1 / 11 (9.09%) 1 | |
| Dermatitis bullous subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 1 / 11 (9.09%) 1 | |
| Dry skin subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 1 / 11 (9.09%) 1 | |
| Erythema multiforme subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 3 | 0 / 11 (0.00%) 0 | |
| Generalised erythema subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 2 | 0 / 11 (0.00%) 0 | |
| Hyperkeratosis | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 11 (9.09%) | |
| occurrences (all) | 0 | 1 | |
| Palmar-plantar erythrodysaesthesia syndrome | | | |
| subjects affected / exposed | 6 / 14 (42.86%) | 1 / 11 (9.09%) | |
| occurrences (all) | 22 | 1 | |
| Pruritus | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 11 (9.09%) | |
| occurrences (all) | 0 | 2 | |
| Rash | | | |
| subjects affected / exposed | 2 / 14 (14.29%) | 1 / 11 (9.09%) | |
| occurrences (all) | 2 | 1 | |
| Rash generalised | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 11 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 11 (9.09%) | |
| occurrences (all) | 0 | 1 | |
| Renal and urinary disorders | | | |
| Dysuria | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 11 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Glycosuria | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 11 (9.09%) | |
| occurrences (all) | 0 | 1 | |
| Haematuria | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 11 (9.09%) | |
| occurrences (all) | 0 | 1 | |
| Proteinuria | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 1 / 11 (9.09%) | |
| occurrences (all) | 1 | 1 | |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 11 (9.09%) | |
| occurrences (all) | 0 | 1 | |
| Endocrine disorders | | | |

| | | | |
|---|----------------------|----------------------|--|
| Hypothyroidism subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 1 | 0 / 11 (0.00%) 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 2 / 11 (18.18%) 2 | |
| Bone pain subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 1 | 1 / 11 (9.09%) 1 | |
| Muscle spasms subjects affected / exposed occurrences (all) | 2 / 14 (14.29%) 2 | 1 / 11 (9.09%) 1 | |
| Musculoskeletal stiffness subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 1 / 11 (9.09%) 1 | |
| Myalgia subjects affected / exposed occurrences (all) | 3 / 14 (21.43%) 4 | 2 / 11 (18.18%) 2 | |
| Pain in extremity subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 1 / 11 (9.09%) 1 | |
| Infections and infestations | | | |
| Abscess oral subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 1 | 0 / 11 (0.00%) 0 | |
| Device related infection subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 1 | 0 / 11 (0.00%) 0 | |
| Enterocolitis infectious subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 2 | 0 / 11 (0.00%) 0 | |
| Genital infection fungal subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 1 / 11 (9.09%) 1 | |
| Laryngitis | | | |

| | | | |
|------------------------------------|-----------------|----------------|--|
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 11 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Oral herpes | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 11 (9.09%) | |
| occurrences (all) | 0 | 1 | |
| Pharyngitis | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 11 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 11 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 11 (9.09%) | |
| occurrences (all) | 0 | 1 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 2 / 14 (14.29%) | 0 / 11 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 11 (9.09%) | |
| occurrences (all) | 0 | 2 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 11 (9.09%) | |
| occurrences (all) | 0 | 2 | |
| Hypertriglyceridaemia | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 11 (9.09%) | |
| occurrences (all) | 0 | 1 | |
| Hyperuricaemia | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 11 (9.09%) | |
| occurrences (all) | 0 | 1 | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 11 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 1 / 11 (9.09%) | |
| occurrences (all) | 2 | 1 | |

| | | | |
|-----------------------------|----------------|----------------|--|
| Hypomagnesaemia | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 11 (9.09%) | |
| occurrences (all) | 0 | 1 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 1 / 11 (9.09%) | |
| occurrences (all) | 1 | 1 | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 1 / 11 (9.09%) | |
| occurrences (all) | 1 | 1 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------|---|
| 08 May 2014 | <ul style="list-style-type: none">- Clarification that the maximum treatment period is up to 2 years (a maximum of 26 Cycles).- Stage 0 gastric cancer added as a permitted prior and concurrent cancer.- An inclusion criterion was modified with respect to previous treatments / treatment duration total length of chemotherapy allowed was extended from 6 to 9 months.- Subjects who present with initial Stage I or II disease and then develop liver metastases and fulfill all of the other eligibility criteria were allowed to be enrolled. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|---------------|---|--------------|
| 05 March 2015 | Early termination of enrollment due to slow enrollment. | - |

Notes:

Limitations and caveats

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

Decimal places were automatically truncated if last decimal equals zero.
This study was prematurely terminated. Analysis was not performed for primary and secondary outcome measures.

Notes: