



Clinical trial results:

A randomised phase II study of Irinotecan, 5-Fluorouracil and Folinic Acid (FOLFIRI) with or without the addition of an endothelin receptor antagonist in patients with metastatic colorectal cancer after failure of Oxaliplatin-containing chemotherapy

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2009-012151-23 |
| Trial protocol | GB |
| Global end of trial date | 27 June 2012 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 (current) |
| This version publication date | 11 January 2022 |
| First version publication date | 11 January 2022 |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | SPON 671-09 |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|----------------|
| ISRCTN number | ISRCTN73199181 |
| ClinicalTrials.gov id (NCT number) | NCT01205711 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Cardiff University |
| Sponsor organisation address | Newport Road, Cardiff, United Kingdom, |
| Public contact | Angela Casbard, Center for Trials Research, casbardac@cardiff.ac.uk |
| Scientific contact | Angela Casbard, Center for Trials Research, casbardac@cardiff.ac.uk |

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 | 26 October 2021 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 27 June 2012 |
| Global end of trial reached? | Yes |
| Global end of trial date | 27 June 2012 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial is to assess whether the addition of ZD4054 to the widely used FOLFIRI chemotherapy regimen improves the clinical outcome for participants with metastatic colorectal cancer who have failed to respond to treatment with oxaliplatin-containing chemotherapy.

Protection of trial subjects:

The IDMC reviewed patient safety data after the first 20 and 40 patients were randomised.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 07 April 2010 |
| 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 | United Kingdom: 111 |
| Worldwide total number of subjects | 111 |
| EEA total number of subjects | 0 |

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) | 72 |
| From 65 to 84 years | 39 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Patients were randomised using a central IWRS system

Pre-assignment

Screening details:

Before any trial related procedures were undertaken, the patient's written informed consent was obtained. The patient was given a minimum of 24 hours after initial invitation to participate before being asked to sign the consent form.

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 | Investigator, Monitor, Carer, Assessor, Subject |

Arms

| | |
|------------------------------|------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Zibotentan |

Arm description:

Originally known as ZD4054

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | zibotentan |
| Investigational medicinal product code | |
| Other name | ZD4054 |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

10mg once a day until disease progression/discontinuation due to toxicity/withdrawal of consent

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

Arm description: -

| | |
|--|----------------------|
| Arm type | Placebo |
| Investigational medicinal product name | placebo - zibotentan |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

once a day until disease progression/discontinuation due to toxicity/withdrawal of consent

| Number of subjects in period 1 | Zibotentan | Placebo |
|---------------------------------------|------------|---------|
| Started | 55 | 56 |
| Completed | 55 | 56 |

Baseline characteristics

Reporting groups

| | |
|--|------------|
| Reporting group title | Zibotentan |
| Reporting group description: Originally known as ZD4054 | |
| Reporting group title | Placebo |
| Reporting group description: - | |

| Reporting group values | Zibotentan | Placebo | Total |
|------------------------|------------|---------|-------|
| Number of subjects | 55 | 56 | 111 |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 37 | 35 | 72 |
| From 65-84 years | 18 | 21 | 39 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 58.8 | 59.7 | |
| standard deviation | ± 11.3 | ± 12.0 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 20 | 23 | 43 |
| Male | 35 | 33 | 68 |

Subject analysis sets

| | |
|--|--------------------|
| Subject analysis set title | Safety Population |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: All patients who received trial treatment | |
| Subject analysis set title | Primary analysis |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: All patient randomised | |

| Reporting group values | Safety Population | Primary analysis | |
|------------------------|-------------------|------------------|--|
| Number of subjects | 108 | 111 | |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 71 | 72 | |
| From 65-84 years | 37 | 39 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 59.2 | 59.7 | |
| standard deviation | ± 11.6 | ± 12.0 | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 42 | 43 | |

| | | | |
|------|----|----|--|
| Male | 66 | 68 | |
|------|----|----|--|

| |
|--|
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| |

End points

End points reporting groups

| | |
|---|--------------------|
| Reporting group title | Zibotentan |
| Reporting group description: | |
| Originally known as ZD4054 | |
| Reporting group title | Placebo |
| Reporting group description: - | |
| Subject analysis set title | Safety Population |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: | |
| All patients who received trial treatment | |
| Subject analysis set title | Primary analysis |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| All patient randomised | |

Primary: Progression Free Survival

| | |
|---|---------------------------|
| End point title | Progression Free Survival |
| End point description: | |
| Progression is defined according to strict radiological criteria (Response Evaluation Criteria in Solid Tumours (RECIST) v 1.1). Lesions will be compared to baseline measurements to assess progression. | |
| End point type | Primary |
| End point timeframe: | |
| Time from enrolment to any disease progression and/or any death | |

| End point values | Zibotentan | Placebo | | |
|---------------------------------------|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 55 | 56 | | |
| Units: months | | | | |
| median (inter-quartile range (Q1-Q3)) | 3.6 (2.1 to 8.2) | 6.8 (3.4 to 9.0) | | |

| | |
|----------------------------|----------------------|
| Attachments (see zip file) | PFS KM Curve/PFS.png |
|----------------------------|----------------------|

Statistical analyses

| | |
|---|----------------------------------|
| Statistical analysis title | Primary analysis - Log rank test |
| Comparison groups | Zibotentan v Placebo |
| Number of subjects included in analysis | 111 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[1] |
| P-value | = 0.0036 ^[2] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.76 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | Other: 80 % |
| sides | 1-sided |
| lower limit | 1.47 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.3752393 |

Notes:

[1] - Designed with One-sided 0.2 alpha in favour of the Zibotentan arm.

[2] - In favour of placebo. The null hypothesis cannot be rejected as it was a one-way test.

Secondary: Overall Survival

| | |
|-----------------|------------------|
| End point title | Overall Survival |
|-----------------|------------------|

End point description:

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

End point timeframe:

Time from randomisation until death or last date seen.

| End point values | Zibotentan | Placebo | | |
|---------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 55 | 56 | | |
| Units: month | | | | |
| median (inter-quartile range (Q1-Q3)) | 11.3 (8.3 to 15.9) | 11.5 (9.0 to 19.5) | | |

Statistical analyses

| | |
|---|----------------------------|
| Statistical analysis title | Summary of Hazard Ratio |
| Comparison groups | Zibotentan v Placebo |
| Number of subjects included in analysis | 111 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.44 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.74 |
| upper limit | 1.96 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.2993883 |

Secondary: Dose reductions

| | |
|-----------------|-----------------|
| End point title | Dose reductions |
|-----------------|-----------------|

End point description:

Number of subjects with dose reductions in each arm

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

End point timeframe:

Dose reductions reported over the trial treatment period

| End point values | Zibotentan | Placebo | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 55 | 56 | | |
| Units: Subjects | | | | |
| Irinotecan | 16 | 17 | | |
| Folinate | 2 | 4 | | |
| 5-FU | 15 | 19 | | |
| Any dose reduction | 18 | 22 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Dose delays

| | |
|-----------------|-------------|
| End point title | Dose delays |
|-----------------|-------------|

End point description:

Number of subjects with any delays to starting any cycle

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

End point timeframe:

During the treatment period

| End point values | Zibotentan | Placebo | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 55 | 56 | | |
| Units: Subjects | 32 | 36 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Withdrawals due to toxicity

| | |
|-----------------|-----------------------------|
| End point title | Withdrawals due to toxicity |
|-----------------|-----------------------------|

End point description:

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

End point timeframe:

Captured at point of treatment discontinuation

| End point values | Zibotentan | Placebo | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 55 | 56 | | |
| Units: Subjects | 7 | 6 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Objective response rate

| | |
|-----------------|-------------------------|
| End point title | Objective response rate |
|-----------------|-------------------------|

End point description:

Patients with complete or partial response as their best response to treatment at any time prior to disease progression or study withdrawal.

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

End point timeframe:

During follow-up

| End point values | Zibotentan | Placebo | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 55 | 56 | | |
| Units: Subjects | 5 | 8 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from randomisation, and during the follow-up period until database lock.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 12.1 |
|--------------------|------|

Reporting groups

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|-----------------------|-----------------------------|
| Reporting group title | Exposed patients Zibotentan |
|-----------------------|-----------------------------|

Reporting group description:

Patients who received trial IMP. 53 participants started trial treatment. 25 patients with SAEs. 53 patients with AEs. ? died.

| | |
|-----------------------|--------------------------|
| Reporting group title | Exposed patients placebo |
|-----------------------|--------------------------|

Reporting group description:

Patients who received trial treatment and placebo

| Serious adverse events | Exposed patients Zibotentan | Exposed patients placebo | |
|---|-----------------------------|--------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 25 / 54 (46.30%) | 18 / 54 (33.33%) | |
| number of deaths (all causes) | 35 | 32 | |
| number of deaths resulting from adverse events | 0 | | |
| Investigations | | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 1 / 54 (1.85%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 1 / 54 (1.85%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Thrombosis in device | | | |
| subjects affected / exposed | 1 / 54 (1.85%) | 0 / 54 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |

| | | | |
|--|-----------------|----------------|--|
| Anaemia | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 1 / 54 (1.85%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 1 / 54 (1.85%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 3 / 54 (5.56%) | 1 / 54 (1.85%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Catheter related complication | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 1 / 54 (1.85%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Death | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 1 / 54 (1.85%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pyrexia | | | |
| subjects affected / exposed | 3 / 54 (5.56%) | 1 / 54 (1.85%) | |
| occurrences causally related to treatment / all | 1 / 5 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 7 / 54 (12.96%) | 2 / 54 (3.70%) | |
| occurrences causally related to treatment / all | 2 / 7 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 3 / 54 (5.56%) | 0 / 54 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|-----------------|--|
| Diarrhoea | | | |
| subjects affected / exposed | 3 / 54 (5.56%) | 6 / 54 (11.11%) | |
| occurrences causally related to treatment / all | 0 / 3 | 2 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 1 / 54 (1.85%) | 1 / 54 (1.85%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 1 / 54 (1.85%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stomatitis | | | |
| subjects affected / exposed | 1 / 54 (1.85%) | 0 / 54 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Swollen tongue | | | |
| subjects affected / exposed | 1 / 54 (1.85%) | 0 / 54 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 54 (1.85%) | 1 / 54 (1.85%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Hydronephrosis | | | |
| subjects affected / exposed | 1 / 54 (1.85%) | 0 / 54 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure acute | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 1 / 54 (1.85%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Urinary retention | | | |
| subjects affected / exposed | 1 / 54 (1.85%) | 0 / 54 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 1 / 54 (1.85%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Back pain | | | |
| subjects affected / exposed | 1 / 54 (1.85%) | 1 / 54 (1.85%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 1 / 54 (1.85%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Biliary tract infection | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 1 / 54 (1.85%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Central line infection | | | |
| subjects affected / exposed | 3 / 54 (5.56%) | 0 / 54 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 1 / 54 (1.85%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenic sepsis | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 1 / 54 (1.85%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Otitis media | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 1 / 54 (1.85%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 3 / 54 (5.56%) | 0 / 54 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Staphylococcal infection | | | |
| subjects affected / exposed | 1 / 54 (1.85%) | 0 / 54 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 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 | Exposed patients Zibotentan | Exposed patients placebo | |
|---|--------------------------------|-----------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 53 / 54 (98.15%) | 53 / 54 (98.15%) | |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 4 / 54 (7.41%) | 3 / 54 (5.56%) | |
| occurrences (all) | 5 | 4 | |
| Phlebitis | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 4 / 54 (7.41%) | |
| occurrences (all) | 0 | 6 | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 10 / 54 (18.52%) | 6 / 54 (11.11%) | |
| occurrences (all) | 16 | 12 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 10 / 54 (18.52%) | 0 / 54 (0.00%) | |
| occurrences (all) | 23 | 0 | |
| Pain | | | |
| subjects affected / exposed | 4 / 54 (7.41%) | 0 / 54 (0.00%) | |
| occurrences (all) | 4 | 0 | |

| | | | |
|--|---|---|--|
| Pyrexia subjects affected / exposed occurrences (all) | 9 / 54 (16.67%) 15 | 10 / 54 (18.52%) 15 | |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) Nasal congestion subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) Rhinorrhoea subjects affected / exposed occurrences (all) | 7 / 54 (12.96%) 10 13 / 54 (24.07%) 28 3 / 54 (5.56%) 10 16 / 54 (29.63%) 49 3 / 54 (5.56%) 3 0 / 54 (0.00%) 0 | 4 / 54 (7.41%) 5 8 / 54 (14.81%) 22 0 / 54 (0.00%) 0 6 / 54 (11.11%) 15 3 / 54 (5.56%) 4 5 / 54 (9.26%) 13 | |
| Psychiatric disorders Confusional state subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all) | 4 / 54 (7.41%) 9 5 / 54 (9.26%) 10 | 0 / 54 (0.00%) 0 0 / 54 (0.00%) 0 | |
| Investigations Blood alkaline phosphatase increased subjects affected / exposed occurrences (all) Neutrophil count decreased subjects affected / exposed occurrences (all) | 3 / 54 (5.56%) 7 27 / 54 (50.00%) 76 | 0 / 54 (0.00%) 0 23 / 54 (42.59%) 66 | |

| | | | |
|---|--|---|--|
| Platelet count decreased subjects affected / exposed occurrences (all) | 10 / 54 (18.52%) 49 | 10 / 54 (18.52%) 72 | |
| White blood cell count decreased subjects affected / exposed occurrences (all) | 23 / 54 (42.59%) 91 | 21 / 54 (38.89%) 77 | |
| Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all) | 0 / 54 (0.00%) 0 | 3 / 54 (5.56%) 4 | |
| Cardiac disorders Chest pain subjects affected / exposed occurrences (all) Sinus tachycardia subjects affected / exposed occurrences (all) | 5 / 54 (9.26%) 10 3 / 54 (5.56%) 3 | 0 / 54 (0.00%) 0 0 / 54 (0.00%) 0 | |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Dysgeusia subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Lethargy subjects affected / exposed occurrences (all) Peripheral sensory neuropathy subjects affected / exposed occurrences (all) | 6 / 54 (11.11%) 14 3 / 54 (5.56%) 7 19 / 54 (35.19%) 49 45 / 54 (83.33%) 224 26 / 54 (48.15%) 117 | 9 / 54 (16.67%) 13 4 / 54 (7.41%) 15 16 / 54 (29.63%) 39 43 / 54 (79.63%) 235 30 / 54 (55.56%) 164 | |
| Blood and lymphatic system disorders Anaemia | | | |

| | | | |
|--|-------------------------|-------------------------|--|
| subjects affected / exposed occurrences (all) | 35 / 54 (64.81%) 216 | 34 / 54 (62.96%) 198 | |
| Eye disorders | | | |
| Lacrimation increased | | | |
| subjects affected / exposed | 6 / 54 (11.11%) | 5 / 54 (9.26%) | |
| occurrences (all) | 23 | 28 | |
| Vision blurred | | | |
| subjects affected / exposed | 6 / 54 (11.11%) | 4 / 54 (7.41%) | |
| occurrences (all) | 19 | 7 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 24 / 54 (44.44%) | 26 / 54 (48.15%) | |
| occurrences (all) | 58 | 72 | |
| Constipation | | | |
| subjects affected / exposed | 27 / 54 (50.00%) | 23 / 54 (42.59%) | |
| occurrences (all) | 94 | 72 | |
| Diarrhoea | | | |
| subjects affected / exposed | 30 / 54 (55.56%) | 36 / 54 (66.67%) | |
| occurrences (all) | 78 | 141 | |
| Dry mouth | | | |
| subjects affected / exposed | 4 / 54 (7.41%) | 3 / 54 (5.56%) | |
| occurrences (all) | 5 | 5 | |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 8 / 54 (14.81%) | |
| occurrences (all) | 0 | 15 | |
| Haemorrhoids | | | |
| subjects affected / exposed | 3 / 54 (5.56%) | 0 / 54 (0.00%) | |
| occurrences (all) | 5 | 0 | |
| Mouth ulceration | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 5 / 54 (9.26%) | |
| occurrences (all) | 0 | 6 | |
| Nausea | | | |
| subjects affected / exposed | 28 / 54 (51.85%) | 24 / 54 (44.44%) | |
| occurrences (all) | 89 | 64 | |
| Rectal discharge | | | |

| | | | |
|---|-------------------------|-------------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 54 (0.00%) 0 | 3 / 54 (5.56%) 8 | |
| Rectal haemorrhage subjects affected / exposed occurrences (all) | 0 / 54 (0.00%) 0 | 3 / 54 (5.56%) 3 | |
| Stomatitis subjects affected / exposed occurrences (all) | 20 / 54 (37.04%) 51 | 25 / 54 (46.30%) 78 | |
| Vomiting subjects affected / exposed occurrences (all) | 14 / 54 (25.93%) 28 | 17 / 54 (31.48%) 31 | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia subjects affected / exposed occurrences (all) | 26 / 54 (48.15%) 108 | 22 / 54 (40.74%) 101 | |
| Hyperhidrosis subjects affected / exposed occurrences (all) | 3 / 54 (5.56%) 7 | 4 / 54 (7.41%) 4 | |
| Nail discolouration subjects affected / exposed occurrences (all) | 0 / 54 (0.00%) 0 | 3 / 54 (5.56%) 5 | |
| Palmar-plantar erythrodysesthesia syndrome subjects affected / exposed occurrences (all) | 5 / 54 (9.26%) 18 | 7 / 54 (12.96%) 10 | |
| Rash maculo-papular subjects affected / exposed occurrences (all) | 8 / 54 (14.81%) 8 | 8 / 54 (14.81%) 41 | |
| Renal and urinary disorders | | | |
| Urinary retention subjects affected / exposed occurrences (all) | 0 / 54 (0.00%) 0 | 3 / 54 (5.56%) 3 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 3 / 54 (5.56%) 8 | 4 / 54 (7.41%) 9 | |
| Back pain | | | |

| | | | |
|---|------------------------|------------------------|--|
| subjects affected / exposed occurrences (all) | 17 / 54 (31.48%) 54 | 13 / 54 (24.07%) 26 | |
| Joint swelling subjects affected / exposed occurrences (all) | 3 / 54 (5.56%) 3 | 0 / 54 (0.00%) 0 | |
| Infections and infestations | | | |
| Catheter related infection subjects affected / exposed occurrences (all) | 4 / 54 (7.41%) 4 | 0 / 54 (0.00%) 0 | |
| Oral herpes subjects affected / exposed occurrences (all) | 0 / 54 (0.00%) 0 | 3 / 54 (5.56%) 3 | |
| Rhinitis subjects affected / exposed occurrences (all) | 4 / 54 (7.41%) 13 | 0 / 54 (0.00%) 0 | |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 54 (0.00%) 0 | 3 / 54 (5.56%) 8 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 14 / 54 (25.93%) 37 | 11 / 54 (20.37%) 32 | |
| Dehydration subjects affected / exposed occurrences (all) | 5 / 54 (9.26%) 5 | 4 / 54 (7.41%) 5 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 21 February 2011 | <p>Amendment to protocol from version 1.1 to 2.0</p> <p>Amendment to the wording of inclusion and exclusion criteria</p> <p>Clarification of treatment descriptions</p> <p>Clarification of dose reduction guidelines</p> <p>Clarification of translational study details and guidelines</p> <p>Clarification of patients assessments</p> |
| 03 August 2011 | <p>The Urgent Safety Measure has been put in place following trial results from another disease area involving the same IMP (ZD4054). Results were released from a trial of ZD4054 in Ovarian Cancer which showed that patients on the ZD4054 arm progressed quicker than those on the Placebo arm. No other trials of ZD4054 showed this same effect. In light of this information, an urgent IDMC meeting was held to review the FOLFERA data on the 27th of July.</p> <p>This showed that in FOLFERA, the ZD4054 arm showed no evidence of benefit. Therefore, an action plan was implemented and agreed with the Sponsor, and this was discussed and agreed with a MHRA Medical Assessor, Dr Carolyn Greenwood.</p> <p>The trial immediately closed to further recruitment and all centres were contacted to request that their patients stop taking the trial drug immediately. Centres were also informed of their patients' unblinding results.</p> <p>We continued collecting follow up data and for patients to continue receiving non-IMP chemotherapy as part of the trial. As such, an additional Participant Information Sheet and Consent Form was produced for patients to re-consent to have this information</p> |

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.

The trial stopped short of its target sample size of 122 due to information about the potential non-efficacy of the drug. The final sample size was 111.

Notes: