



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
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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	Subject, Investigator, Monitor, Carer, Assessor

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
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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
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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
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End point description:

End point type	Secondary
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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
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End point description:

Number of subjects with dose reductions in each arm

End point type	Secondary
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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
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End point description:

Number of subjects with any delays to starting any cycle

End point type	Secondary
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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
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End point description:

End point type	Secondary
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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
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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
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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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	12.1
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Reporting groups

Reporting group title	Exposed patients Zibotentan
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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
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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 occurrences (all)	6 / 54 (11.11%) 23	5 / 54 (9.26%) 28	
Vision blurred subjects affected / exposed occurrences (all)	6 / 54 (11.11%) 19	4 / 54 (7.41%) 7	
Gastrointestinal disorders			
Abdominal pain subjects affected / exposed occurrences (all)	24 / 54 (44.44%) 58	26 / 54 (48.15%) 72	
Constipation subjects affected / exposed occurrences (all)	27 / 54 (50.00%) 94	23 / 54 (42.59%) 72	
Diarrhoea subjects affected / exposed occurrences (all)	30 / 54 (55.56%) 78	36 / 54 (66.67%) 141	
Dry mouth subjects affected / exposed occurrences (all)	4 / 54 (7.41%) 5	3 / 54 (5.56%) 5	
Dyspepsia subjects affected / exposed occurrences (all)	0 / 54 (0.00%) 0	8 / 54 (14.81%) 15	
Haemorrhoids subjects affected / exposed occurrences (all)	3 / 54 (5.56%) 5	0 / 54 (0.00%) 0	
Mouth ulceration subjects affected / exposed occurrences (all)	0 / 54 (0.00%) 0	5 / 54 (9.26%) 6	
Nausea subjects affected / exposed occurrences (all)	28 / 54 (51.85%) 89	24 / 54 (44.44%) 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 erythrodysaesthesia 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: