Clinical trial results:
A randomised controlled phase II trial of oral vinorelbine as second line therapy for patients with malignant pleural mesothelioma

Summary

EudraCT number	2014-001992-30
Trial protocol	GB
Global end of trial date	08 September 2022

Results information

Result version number	v1 (current)
This version publication date	22 September 2023
First version publication date	22 September 2023
Summary attachment (see zip file)	VIM manuscript eClinMed (VIM manuscript eClinical Medicine.pdf)

Trial information

Trial identification

Sponsor protocol code	UNOLE 0329

Additional study identifiers

ISRCTN number	ISRCTN44518069
ClinicalTrials.gov id (NCT number)	NCT02139904
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Leicester
Sponsor organisation address	Research Governance Office, Academic Department, Leicester General Hospital, Leicester, United Kingdom, LE5 4PW
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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	17 March 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 March 2021
Global end of trial reached?	Yes
Global end of trial date	08 September 2022
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 determine whether treatment with vinorelbine in patients with malignant mesothelioma improves overall survival.

Protection of trial subjects:

Regular IDMC meetings were held for review of safety and recruitment

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 June 2015
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: 154
Worldwide total number of subjects	154
EEA total number of subjects	154

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)	36
From 65 to 84 years	117
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

225 patients were screened. 48 were ineligible: 27 did not meet inclusion criteria, 5 died and 16 for unknown reasons. 23 were eligible but not randomised: 17 declined to participate,1 entered an alternative trial, 1 was unwilling to travel and 4 for unknown reasons.

Pre-assignment period milestones

Number of subjects started	154
Number of subjects completed	154

Period 1

Period 1 title	Treatment (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	ASC alone

Arm description:

Standard of care treatment only

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	ASC plus vinorelbine

Arm description:

Standard of care plus vinorelbine

Arm type	Experimental
Investigational medicinal product name	Vinorelbine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Vinorelbine was administered at a dose of 60mg/m2 orally weekly for the first cycle (days 1, 8 and 15) on a 3-weekly cycle. Subsequent doses could be increased to 80mg/m2 (day 22) if there had been no haematological toxicity (neutrophil count dropped once below 0.5 x 109/L or more than once between 0.5 and 1.0 x 109/L during the first three administrations at 60mg/m^2). Even for patients with BSA > 2 m2 the total dose should never exceed 120 mg per week at 60 mg /m2 and 160 mg per week at 80 mg/m2. Dosing continued on a weekly schedule until progression or unacceptable toxicity.

Number of subjects in period 1	ASC alone	ASC plus vinorelbine
Started	56	98
Completed	49	87
Not completed	7	11
Consent withdrawn by subject	4	1
Physician decision	1	2
Adverse event, non-fatal	-	3
Unknown	-	1
Lost to follow-up	2	4

Baseline characteristics

Reporting groups	
Reporting group title	ASC alone
Reporting group description: Standard of care treatment only	
Reporting group title	ASC plus vinorelbine
Reporting group description: Standard of care plus vinorelbine	

Reporting group values	ASC alone	ASC plus vinorelbine	Total
Number of subjects	56	98	154
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
median	70.7	70.5	
inter-quartile range (Q1-Q3)	66.6 to 74.2	65.4 to 76.4	-
Gender categorical Units: Subjects			
Female	11	18	29
Male	45	80	125
ECOG Performance status Units: Subjects			
Zero	12	26	38
One	44	71	115
Missing		1	1
Mesothelioma type Units: Subjects			
Epithelioid	48	81	129
Biphasic or sarcomatoid	3	13	16
NOS	5	3	8
Missing	0	1	1
Best response during first line therapy Units: Subjects			
DCR (Complete response, partial response or stable	40	73	113
Progressive disease	16	24	40
Missing	0	1	1

Smoking status Units: Subjects			
Smoker	2	6	8
Non-smoker	19	40	59
Ex-smoker	34	52	86
Missing	1	0	1
Asbestos history Units: Subjects			
Yes	47	80	127
No	6	17	23
Missing	3	1	4
T stage Units: Subjects			
T1	8	10	18
T2	13	10	23
T3	21	35	56
T4	12	37	49
Tis	0	1	1
TX	1	1	2
Missing	1	4	5
N stage Units: Subjects			
N0	26	49	75
N1	11	8	19
N2	15	32	47
N3	2	4	6
NX	1	1	2
Missing	1	4	5
M stage Units: Subjects			
M0	46	77	123
M1	7	15	22
Missing	3	6	9
Extra-thoracic metastases Units: Subjects			
Yes	5	7	12
No	50	89	139
Missing	1	2	3
BSA Units: kg/m^2			
median	1.9	1.9	
inter-quartile range (Q1-Q3)	1.8 to 2.0	1.8 to 2.1	-

Subject analysis sets

Subject analysis set title	ASC alone
Subject analysis set type	Intention-to-treat
Subject analysis set description: Patients to receive active symptom control only	
Subject analysis set title	ASC plus vinorelbine
Subject analysis set type	Intention-to-treat

Subject analysis set description:
Patients to receive active symptom control and vinorelbine

Reporting group values	ASC alone	ASC plus vinorelbine	
Number of subjects	56	98	
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
median	70.7	70.5	
inter-quartile range (Q1-Q3)	66.6 to 74.2	65.4 to 76.4	
Gender categorical Units: Subjects			
Female	11	18	
Male	45	80	
ECOG Performance status Units: Subjects			
Zero	12	26	
One	44	71	
Missing		1	
Mesothelioma type Units: Subjects			
Epithelioid	48	81	
Biphasic or sarcomatoid	3	13	
NOS	5	3	
Missing	0	1	
Best response during first line therapy Units: Subjects			
DCR (Complete response, partial response or stable	40	73	
Progressive disease	16	24	
Missing	0	1	
Smoking status Units: Subjects			
Smoker	2	6	
Non-smoker	19	40	
Ex-smoker	34	52	
Missing	1	0	
Asbestos history Units: Subjects			
Yes	47	80	

No	6	17	
Missing	3	1	
T stage Units: Subjects			
T1	8	10	
T2	13	10	
T3	21	35	
T4	12	37	
Tis	0	1	
TX	1	1	
Missing	1	4	
N stage Units: Subjects			
N0	26	49	
N1	11	8	
N2	15	32	
N3	2	4	
NX	1	1	
Missing	1	4	
M stage Units: Subjects			
M0	46	77	
M1	7	15	
Missing	3	6	
Extra-thoracic metastases Units: Subjects			
Yes	5	7	
No	50	89	
Missing	1	2	
BSA Units: kg/m^2			
median	1.9	1.9	
inter-quartile range (Q1-Q3)	1.8 to 2.0	1.8 to 2.1	

End points

End points reporting groups	
Reporting group title	ASC alone
Reporting group description: Standard of care treatment only	
Reporting group title	ASC plus vinorelbine
Reporting group description: Standard of care plus vinorelbine	
Subject analysis set title	ASC alone
Subject analysis set type	Intention-to-treat
Subject analysis set description: Patients to receive active symptom control only	
Subject analysis set title	ASC plus vinorelbine
Subject analysis set type	Intention-to-treat
Subject analysis set description: Patients to receive active symptom control and vinorelbine	

Primary: Progression-free survival	
End point title	Progression-free survival
End point description:	
End point type	Primary
End point timeframe: Time from randomisation to any disease progression and/or any death, defined according to Modified RECIST. Patients who were event free will be censored at the date of their last evaluable RECIST assessment.	

End point values	ASC alone	ASC plus vinorelbine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	56	98		
Units: Time to event (months)				
median (inter-quartile range (Q1-Q3))	2.8 (1.4 to 4.1)	4.2 (2.2 to 8)		

Statistical analyses

Statistical analysis title	Progression-free survival
Comparison groups	ASC alone v ASC plus vinorelbine
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0022
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	0.86

Secondary: Overall survival

End point title	Overall survival
End point description:	

End point type	Secondary
End point timeframe:	
From randomisation to death	

End point values	ASC alone	ASC plus vinorelbine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	56	98		
Units: Time from randomization to death (months				
median (inter-quartile range (Q1-Q3))	9.1 (5.7 to 14.1)	9.3 (6.7 to 11.8)		

Statistical analyses

Statistical analysis title	Overall survival
Comparison groups	ASC alone v ASC plus vinorelbine
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.237
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	1.17

Secondary: Objective response

End point title	Objective response

End point description:

End point type	Secondary

End point timeframe:

Best response from randomisation to end of follow up

End point values	ASC alone	ASC plus vinorelbine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	56	98		
Units: Subjects				
Complete response	0	1		
Partial response	2	4		
Stable disease	25	60		
Progressive disease	17	18		
Did not reach first assessment time point	7	8		
Missing	5	7		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective response rate

End point title	Objective response rate

End point description:

Objective response rate (ORR) will be based on Modified RECIST. ORR is defined as the proportion of participants whose best response was complete response (CR) or partial response (PR)

End point type	Secondary

End point timeframe:

From randomisation to end of follow up

End point values	ASC alone	ASC plus vinorelbine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	56	98		
Units: Subjects				
Complete response/partial response	2	5		

Statistical analyses

Statistical analysis title	Objective response rate odds ratio
Comparison groups	ASC alone v ASC plus vinorelbine
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.89
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.14
upper limit	5.51

Secondary: Clinical benefit rate	
End point title	Clinical benefit rate
End point description:	
CBR (also referred to as disease control rate (DCR)) will be defined as the proportion of patients with CR, PR or stable disease (SD) at 12 weeks	
End point type	Secondary
End point timeframe:	
From randomisation to end of follow up	

End point values	ASC alone	ASC plus vinorelbine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	56	98		
Units: Subjects				
CR, PR or stable disease	27	65		

Statistical analyses

Statistical analysis title	Clinical benefit rate odds ratio
Comparison groups	ASC alone v ASC plus vinorelbine
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.04
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.09

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.03
upper limit	4.24

Secondary: Duration of response overall

End point title	Duration of response overall

End point description:

End point type	Secondary

End point timeframe:

From randomisation to end of follow up

End point values	ASC alone	ASC plus vinorelbine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	56	98		
Units: Time (months)				
median (inter-quartile range (Q1-Q3))	3.5 (2.8 to 4.2)	7.2 (3.9 to 8.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of partial response

End point title	Duration of partial response

End point description:

End point type	Secondary

End point timeframe:

From randomisation to end of follow up

End point values	ASC alone	ASC plus vinorelbine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	56	98		
Units: Time (months)				
median (inter-quartile range (Q1-Q3))	3.5 (2.8 to 4.2)	7.8 (5.1 to 11.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of stable disease

End point title	Duration of stable disease

End point description:

End point type	Secondary

End point timeframe:

From randomisation to end of follow up

End point values	ASC alone	ASC plus vinorelbine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	56	98		
Units: Time (months)				
median (inter-quartile range (Q1-Q3))	3.7 (2.8 to 4.2)	4.2 (2.8 to 5.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response according to ORR

End point title	Duration of response according to ORR

End point description:

End point type	Secondary

End point timeframe:

From randomisation to end of follow up

End point values	ASC alone	ASC plus vinorelbine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	56	98		
Units: Time (months)				
median (inter-quartile range (Q1-Q3))	3.5 (2.8 to 4.2)	7.2 (3.9 to 8.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response according to clinical benefit rate

End point title	Duration of response according to clinical benefit rate

End point description:

End point type	Secondary

End point timeframe:

From randomisation to end of follow up

End point values	ASC alone	ASC plus vinorelbine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	56	98		
Units: Time (months)				
median (inter-quartile range (Q1-Q3))	3.7 (2.8 to 4.2)	4.2 (2.8 to 6.9)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From randomisation to end of follow up	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	12.1
Reporting groups	
Reporting group title	ASC alone - safety population
Reporting group description: -	
Reporting group title	ASC plus vinorelbine-safety population
Reporting group description: -	

Serious adverse events	ASC alone - safety population	ASC plus vinorelbine-safety population	
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 51 (19.61%)	31 / 96 (32.29%)	
number of deaths (all causes)	38	70	
number of deaths resulting from adverse events	2	2	
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	0 / 51 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 51 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 51 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac other: Blocked IVC and SVC			

subjects affected / exposed	1 / 51 (1.96%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Motor neuropathy			
subjects affected / exposed	1 / 51 (1.96%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiculitis brachial			
subjects affected / exposed	1 / 51 (1.96%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 51 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 51 (0.00%)	3 / 96 (3.13%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 51 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fever			
subjects affected / exposed	0 / 51 (0.00%)	2 / 96 (2.08%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 51 (0.00%)	2 / 96 (2.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 51 (0.00%)	2 / 96 (2.08%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 51 (1.96%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 51 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 51 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 51 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 51 (1.96%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 51 (0.00%)	5 / 96 (5.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	1 / 51 (1.96%)	2 / 96 (2.08%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 1	1 / 1	
Pneumothorax			
subjects affected / exposed	1 / 51 (1.96%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 51 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	0 / 51 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infection			
subjects affected / exposed	0 / 51 (0.00%)	3 / 96 (3.13%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	3 / 51 (5.88%)	5 / 96 (5.21%)	
occurrences causally related to treatment / all	0 / 3	1 / 5	
deaths causally related to treatment / all	0 / 1	1 / 1	
Neutropenic sepsis			
subjects affected / exposed	0 / 51 (0.00%)	2 / 96 (2.08%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 51 (0.00%)	2 / 96 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 51 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	ASC alone - safety population	ASC plus vinorelbine-safety population	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 51 (58.82%)	81 / 96 (84.38%)	
Investigations			
Weight decreased			
subjects affected / exposed	3 / 51 (5.88%)	6 / 96 (6.25%)	
occurrences (all)	4	12	
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 51 (5.88%)	8 / 96 (8.33%)	
occurrences (all)	5	9	
Nervous system disorders			
Sensory neuropathy			
subjects affected / exposed	1 / 51 (1.96%)	7 / 96 (7.29%)	
occurrences (all)	4	16	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 51 (9.80%)	23 / 96 (23.96%)	
occurrences (all)	7	86	
Lymphopenia			
subjects affected / exposed	2 / 51 (3.92%)	16 / 96 (16.67%)	
occurrences (all)	3	33	
Neutropenia			
subjects affected / exposed	0 / 51 (0.00%)	18 / 96 (18.75%)	
occurrences (all)	0	29	
General disorders and administration site conditions			
Fatigue			

subjects affected / exposed	11 / 51 (21.57%)	50 / 96 (52.08%)	
occurrences (all)	34	146	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 51 (1.96%)	15 / 96 (15.63%)	
occurrences (all)	1	34	
Constipation			
subjects affected / exposed	4 / 51 (7.84%)	38 / 96 (39.58%)	
occurrences (all)	5	59	
Diarrhoea			
subjects affected / exposed	2 / 51 (3.92%)	24 / 96 (25.00%)	
occurrences (all)	3	40	
Flatulence			
subjects affected / exposed	1 / 51 (1.96%)	7 / 96 (7.29%)	
occurrences (all)	1	20	
Nausea			
subjects affected / exposed	2 / 51 (3.92%)	22 / 96 (22.92%)	
occurrences (all)	6	46	
Vomiting			
subjects affected / exposed	2 / 51 (3.92%)	9 / 96 (9.38%)	
occurrences (all)	2	11	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	12 / 51 (23.53%)	21 / 96 (21.88%)	
occurrences (all)	24	32	
Dyspnoea			
subjects affected / exposed	9 / 51 (17.65%)	31 / 96 (32.29%)	
occurrences (all)	26	83	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 51 (1.96%)	10 / 96 (10.42%)	
occurrences (all)	1	31	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 51 (3.92%)	7 / 96 (7.29%)	
occurrences (all)	4	16	

Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 51 (5.88%)	11 / 96 (11.46%)	
occurrences (all)	5	18	
Chest pain			
subjects affected / exposed	5 / 51 (9.80%)	14 / 96 (14.58%)	
occurrences (all)	10	24	
Infections and infestations			
Infection			
subjects affected / exposed	2 / 51 (3.92%)	7 / 96 (7.29%)	
occurrences (all)	2	7	
Lower respiratory tract infection			
subjects affected / exposed	6 / 51 (11.76%)	11 / 96 (11.46%)	
occurrences (all)	8	13	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	5 / 51 (9.80%)	22 / 96 (22.92%)	
occurrences (all)	8	55	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 March 2015	Amendment to protocol V2 Additional sites: University Hospital Southampton NHS Foundation Trust, Newcastle Upon Tyne Hospitals NHS Foundation Trust, Brighton & Sussex Univ. Hospitals NHS Trust, University Hospital of North Midlands NHS Trust. Change of PI from Dr Noelle O'Rourke to Dr Nicole Steele at The Beatson REC Approval 10/03/2015 HRA Approval 4/4/2016
06 March 2015	Protocol V2.0 – V3.0. Inclusion criteria no 1 modified. Drug Supply, Distribution and Storage section updated. REC approval 13/04/2015 Not submitted to HRA MHRA rejected 02/04/2015
15 April 2015	Protocol V3.0 – V4.0. Two new exclusion criteria added, One existing exclusion criteria updated. A section has been removed from Medications/Procedures permitted with caution, and moved to Non-permitted concomitant medications/procedures. Pregnancy has been added as a withdrawal reason. REC approval 18/05/2015 Not submitted to HRA MHRA approval 20/04/2015
16 November 2015	Protocol V4.0 – V5.0. Widespread updates to the protocol, see amendment log. GP letter V1.0 – V2.0. Addition of permitted and non-permitted medications/procedures, and possible drug interactions. REC approval 30/11/2015 MHRA approval 15/12/2015
17 January 2017	Protocol V5.0 – 6.0. Exclusion Criteria no 2 from protocol V5.0 removed for Protocol V6.0. Trial staff changes. Safety reporting procedures and randomisation number changed. Minor typo errors. Modified RECIST has been clarified. PIS V3.0 – V4.0. Tests that a patient may receive has been changed from a list to a more generalised paragraph as recommended by the Pt Rep on the TMG. MHRA rejected 20/02/2017
12 April 2017	Addition of: University Hospitals of Morecambe Bay NHS Foundation Trust REC approval26/04/2017 HRA approval 02/05/2017

21 April 2017	Protocol V6.0 – 7.0 Exclusion Criteria no 2 (to remove 30 day wash out period for drugs) which was removed for protocol V6 and was rejected by MHRA has now been added back in to the protocol as requested by the MHRA. MHRA also rejected a change of neutrophil count so the neutrophil count is back to its original value as when it was initially approved by the MHRA. Ethics approved both protocol and PIS but these will both be resubmitted again due to the protocol version number will have to change to V7.0 REC approval 12/05/2017 HRA approval 19/06/2017 MHRA approval 08/06/2017
03 July 2017	Additional site Shrewsbury and Telford NHS Trust REC approval 3/7/2017 HRA approval 11/07/2017
21 July 2017	Additional site Derby and Teaching Hospitals NHS foundation Trust REC approval 25/07/17 HRA approval 10/08/17
22 September 2017	Addition of Southend University Hospital
30 April 2018	Change of PI from Dr Marianne Nicholson to Dr Gillian Price at Aberdeen Royal Infirmary
10 September 2018	Protocol V8.0 change of endpoint from OS to PFS REC approval 12/10/18 HRA approval 22/10/18 MHRA approval 8/10/18

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/35706488