Clinical trial results:
VIP: A prospective, phase II, double blinded, multicentre, randomised clinical trial comparing combination gemcitabine and vandetanib therapy with gemcitabine therapy alone in locally advanced or metastatic pancreatic carcinoma.

Summary

EudraCT number	2010-021951-26
Trial protocol	GB
Global end of trial date	05 September 2018

Results information

Result version number	v1 (current)
This version publication date	18 December 2019
First version publication date	18 December 2019

Trial information

Trial identification

Sponsor protocol code	UoL000621/R&D3963

Additional study identifiers

ISRCTN number	ISRCTN74555382
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Liverpool
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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	No

1901/2006 apply to this trial?	

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 January 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 September 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess whether overall survival time using gemcitabine plus vandetanib is longer than that using gemcitabine alone as the first treatment for advanced or metastatic pancreatic cancer.

Protection of trial subjects:

Central and on-site monitoring was conducted to help protect patients and to monitor performance relating to trial procedures, trial intervention, administration and laboratory/data collection processes. A risk assessment was carried out to determine the level of monitoring required and subsequently a monitoring plan was developed to document how and when monitoring is conducted and to what extent. Patient safety data was monitored via LCTU pharmacovigilance procedures (reporting and review of adverse event data) and by an ISDMC.

A Trial Management Group regularly reviewed central monitoring reports and advised accordingly.

Serious adverse events were followed up until resolution or death. Annual safety reports were submitted to the national regulatory authorities.

Background therapy: -

Evidence for comparator:

For patients with locally advanced or metastatic pancreatic carcinoma who wish to have and are fit enough to benefit from active treatment, chemotherapy with single agent gemcitabine has for several years been the standard of care. The only trial to demonstrate an incremental improvement in efficacy for the addition of another drug to the gemcitabine/erlotinib combination is AVITA (conducted in patients with metastatic disease alone). Although this trial failed to reach its primary end point of improved OS with the addition of bevacizumab, PFS was significantly prolonged and there was a strong trend for improved response rate. Thus, there is a strong clinical evidence-based rationale for building upon and further investigating the impact of dual EGFR and VEGFR blockade in pancreatic cancer. Vandetanib inhibits a third tyrosine kinase and this may significantly augment the therapeutic impact of dual VEGRF/EGFR inhibition in pancreatic cancer.

In this trial vandetanib is combined with gemcitabine and outcome compared with gemcitabine alone, given that gemcitabine monotherapy remains a regulatory standard of care and a globally accepted trial comparator. After discussion with Vandetanib team at Astra Zeneca an initial dose of 300mg/day of vandetanib in combination with gemcitabine was selected for use in the VIP study. Therefore half of the patients on the study were treated with an oral placebo alongside gemcitabine and the other half received vandetanib alongside gemcitabine.

Actual start date of recruitment	01 September 2011
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: 142
Worldwide total number of subjects	142
EEA total number of subjects	142

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)	60
From 65 to 84 years	82
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

UK only. The ViP study recruited 142 patients across 18 centres across England and Northern Ireland between 24 October 2011 and 09 October 2013. First patient, first visit (FPFV; date of randomisation): 24 October 2011. Follow up data included up to 15 July 2015.

Pre-assignment

Screening details:

142 of the 382 patients screened were recruited to the study. Screening: Informed consent; Histology/Cytology; Demography & medical history; Concomitant medication; Physical examination & medical review; ECOG; 12-lead ECG; CT scan chest, abdomen & pelvis; Haematological/Clinical Chemistry; Vital signs; Translational bloods; CA19-9; pregnancy test.

Period 1

Period 1 title	Treatment phase (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Blinding implementation details:

VIP is designed as a double blinded trial with clinicians and all members of the trial management team being blind to which treatment a patient is randomised to. Members of the DMC shall be un-blind to enable them to assess the performance of the trial. The VIP Trial Statistician is partially un-blind and will receive a 0/1 indicator to differentiate between the two treatments (without being made aware of what 0/1 represent) so they can produce reports.

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A: Placebo plus Gemcitabine

Arm description:

Placebo orally once a day continuously together with Gemcitabine 1000mg/m2 weekly as a 30 minute infusion for 7 consecutive weeks, followed by a one week break, followed by Gemcitabine 1000mg/m2 weekly as a 30 minute infusion for 3 weeks followed by a one week break in subsequent cycles

Arm type	Placebo plus IMP
Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	Gemzar
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1000mg/m2 must be given as an intravenous infusion over 30 minutes unless haematological toxicity occurs requiring dose adjustment.

Arm title	Arm B: Vandetanib plus Gemcitabine

Arm description:

Vandetanib orally once a day continuously together with Gemcitabine 1000mg/m2 weekly as a 30 minute infusion for 7 consecutive weeks, followed by a one week break, followed by Gemcitabine 1000mg/m2 weekly as a 30 minute infusion for 3 weeks followed by a one week break in subsequent cycles.

Arm type	Experimental
Investigational medicinal product name	Vandetanib
Investigational medicinal product code	
Other name	ZD6474
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
300 mg once a day continuously.

Number of subjects in period 1	Arm A: Placebo plus Gemcitabine	Arm B: Vandetanib plus Gemcitabine
Started	70	72
Completed	69	68
Not completed	1	4
Symptomatic deterioration	-	1
Patient became ill for treatment at randomisation	1	1
Patient stopped treatment	-	1
Clinical deterioration	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Arm A: Placebo plus Gemcitabine
Reporting group description:	
Placebo orally once a day continuously together with Gemcitabine 1000mg/m2 weekly as a 30 minute infusion for 7 consecutive weeks, followed by a one week break, followed by Gemcitabine 1000mg/m2 weekly as a 30 minute infusion for 3 weeks followed by a one week break in subsequent cycles	
Reporting group title	Arm B: Vandetanib plus Gemcitabine
Reporting group description:	
Vandetanib orally once a day continuously together with Gemcitabine 1000mg/m2 weekly as a 30 minute infusion for 7 consecutive weeks, followed by a one week break, followed by Gemcitabine 1000mg/m2 weekly as a 30 minute infusion for 3 weeks followed by a one week break in subsequent cycles.	

Reporting group values	Arm A: Placebo plus Gemcitabine	Arm B: Vandetanib plus Gemcitabine	Total
Number of subjects	70	72	142
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
median	67.5	66.5	
inter-quartile range (Q1-Q3)	61 to 73	61 to 73	-
Gender categorical			
Units: Subjects			
Female	40	43	83
Male	30	29	59
Ethnicity			
Units: Subjects			
White	60	67	127
Asian	4	3	7
Black	3	0	3
Other	3	2	5
Tumour Histology			
Units: Subjects			
Pancreatic ductal adenocarcinoma	62	66	128
Undiff. carcinoma of the pancreas	8	6	14
Tumour Site			
Units: Subjects			
Body	13	24	37
Head	47	31	78
Tail	5	13	18
Uncinate	5	4	9
Tumour Differentiation			
Units: Subjects			
Well	7	6	13
Moderate	12	16	28
Poor	14	12	26
Undifferentiated	1	4	5

Unknown	29	30	59
Cannot be assessed	7	4	11
Smoking status			
Units: Subjects			
Current Smoker	10	19	29
Ex smoker	23	30	53
Never Smoked	34	20	54
Not recorded	3	3	6
ECG			
Units: IQR			
median	426	418.5	
inter-quartile range (Q1-Q3)	408.25 to 436.75	399 to 435.75	-
Haemoglobin			
Units: g/dl			
median	12.93	12.7	
inter-quartile range (Q1-Q3)	11.9 to 13.575	11.775 to 13.525	-
WBC			
Units: 10/L			
median	7.67	7.88	
inter-quartile range (Q1-Q3)	6.275 to 10.475	6.777 to 9.65	-
Neutrophils			
Units: 10*9/L			
median	4.95	5.185	
inter-quartile range (Q1-Q3)	4.047 to 6.65	4.3 to 6.85	-
Lymphocytes			
Units: 10*9/L			
median	1.6	1.4	
inter-quartile range (Q1-Q3)	1.2 to 2.055	1.1 to 2.145	-
Platelets			
Units: 10*9/L			
median	240.5	246.5	
inter-quartile range (Q1-Q3)	198 to 297	200.5 to 315.5	-
Albumin			
Units: g/L			
median	40	40	
inter-quartile range (Q1-Q3)	37 to 44.75	37 to 43	-
Blood Urea			
Units: mmol/L			
median	4.65	4.35	
inter-quartile range (Q1-Q3)	3.825 to 6.175	3.7 to 5.6	-
Bilirubin			
Units: ymol/L			
median	8	8	
inter-quartile range (Q1-Q3)	6 to 12.75	6.75 to 12	-
Potassium			
Units: mmol/L			
median	4.4	4.5	
inter-quartile range (Q1-Q3)	4.2 to 4.6	4.3 to 4.7	-
Corr'c Calcium			
Units: mmol/L			
median	2.385	2.355	
inter-quartile range (Q1-Q3)	2.33 to 2.46	2.28 to 2.422	-

Serum Creatinine Units: umol/L median inter-quartile range (Q1-Q3)	 71.5 61.25 to 80	 65 58.5 to 73.25	 -
Sodium Units: mmol/L median inter-quartile range (Q1-Q3)	 138 136 to 140	 138 135 to 140	 -
y-GT Units: U/L median inter-quartile range (Q1-Q3)	 86 43 to 251	 69 35.75 to 158.25	 -
CA19-9 Units: KU/L median inter-quartile range (Q1-Q3)	 1259.5 264.75 to 6080.25	 1018 199 to 6104	 -
ALT Units: U/L median inter-quartile range (Q1-Q3)	 28.5 22.25 to 39.5	 23.5 16 to 40	 -

End points

End points reporting groups

Reporting group title	Arm A: Placebo plus Gemcitabine

Reporting group description:

Placebo orally once a day continuously together with Gemcitabine 1000mg/m2 weekly as a 30 minute infusion for 7 consecutive weeks, followed by a one week break, followed by Gemcitabine 1000mg/m2 weekly as a 30 minute infusion for 3 weeks followed by a one week break in subsequent cycles

Reporting group title	Arm B: Vandetanib plus Gemcitabine

Reporting group description:

Vandetanib orally once a day continuously together with Gemcitabine 1000mg/m2 weekly as a 30 minute infusion for 7 consecutive weeks, followed by a one week break, followed by Gemcitabine 1000mg/m2 weekly as a 30 minute infusion for 3 weeks followed by a one week break in subsequent cycles.

Primary: Overall Survival

End point title	Overall Survival

End point description:

Participants were assessed whether overall survival time using gemcitabine plus vandetanib is longer than that using gemcitabine alone as first line treatment for advanced pancreatic cancer.

End point type	Primary

End point timeframe:

Time is measured from randomisation to death from any cause.

End point values	Arm A: Placebo plus Gemcitabine	Arm B: Vandetanib plus Gemcitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	72		
Units: months				
median (confidence interval 95%)	8.95 (6.55 to 11.74)	8.83 (7.11 to 11.58)		

Statistical analyses

Statistical analysis title	OS - Cox Model

Statistical analysis description:

A stratified Cox regression with 6 strata defined by Stage of disease (locally advanced vs. metastatic) and ECOG Performance status (0 versus 1 versus 2) at baseline.

Comparison groups	Arm A: Placebo plus Gemcitabine v Arm B: Vandetanib plus Gemcitabine

Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.301
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.95
upper limit	1.53

Secondary: Progression-free survival

End point title	Progression-free survival

End point description:

Comparison between the two treatment arms for progression-free survival.

End point type	Secondary

End point timeframe:

From randomisation until progression or death from any cause.

End point values	Arm A: Placebo plus Gemcitabine	Arm B: Vandetanib plus Gemcitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	72		
Units: months				
median (confidence interval 95%)	6.09 (5 to 9.9)	8.04 (4.54 to 10.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective response rate

End point title	Objective response rate

End point description:

Comparison between the two treatment arms for overall response rate.

End point type	Secondary

End point timeframe:

From randomisation until death by any cause.

End point values	Arm A: Placebo plus Gemcitabine	Arm B: Vandetanib plus Gemcitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	40		
Units: subjects	9	10		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease control rate

End point title	Disease control rate

End point description:

Comparison between the two treatment arms for disease control, assessed by CT scans per RECIST version 1.1.

End point type	Secondary

End point timeframe:

From randomisation until death from any cause.

End point values	Arm A: Placebo plus Gemcitabine	Arm B: Vandetanib plus Gemcitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	42		
Units: subjects	10	8		

Statistical analyses

No statistical analyses for this end point

Secondary: Patient pain assessment

End point title	Patient pain assessment

End point description:

Comparison between the two treatment arms for patient pain assessment.

End point type	Secondary

End point timeframe:

From randomisation until death from any cause.

End point values	Arm A: Placebo plus Gemcitabine	Arm B: Vandetanib plus Gemcitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	72		
Units: Patients				
median (confidence interval 95%)				
Day 1	30 (9.5 to 50)	30 (5 to 50)		
3 Month	5.5 (0 to 30)	5 (0 to 30)		
6 Month	10 (0 to 29)	1.5 (0 to 35)		
12 Month	16 (4 to 18.5)	15 (4.25 to 20.25)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Reporting period is patient on study and up to 30 days post last dose of trial treatment

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4

Reporting groups

Reporting group title	Arm A: Placebo plus Gemcitabine

Reporting group description:

Placebo orally once a day continuously together with Gemcitabine 1000mg/m2 weekly as a 30 minute infusion for 7 consecutive weeks, followed by a one week break, followed by Gemcitabine 1000mg/m2 weekly as a 30 minute infusion for 3 weeks followed by a one week break in subsequent cycles.

Reporting group title	Arm B: Vandetanib plus Gemcitabine

Reporting group description:

Vandetanib orally once a day continuously together with Gemcitabine 1000mg/m2 weekly as a 30 minute infusion for 7 consecutive weeks, followed by a one week break, followed by Gemcitabine 1000mg/m2 weekly as a 30 minute infusion for 3 weeks followed by a one week break in subsequent cycles.

Serious adverse events	Arm A: Placebo plus Gemcitabine	Arm B: Vandetanib plus Gemcitabine	
Total subjects affected by serious adverse events			
subjects affected / exposed	42 / 70 (60.00%)	50 / 72 (69.44%)	
number of deaths (all causes)	61	70	
number of deaths resulting from adverse events	6	7	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 70 (1.43%)	2 / 72 (2.78%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	3 / 70 (4.29%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	3 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thromboembolic event			
subjects affected / exposed	6 / 70 (8.57%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	5 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

General disorders and administration site conditions			
Chills			
subjects affected / exposed	4 / 70 (5.71%)	3 / 72 (4.17%)	
occurrences causally related to treatment / all	3 / 5	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Edema limbs			
subjects affected / exposed	2 / 70 (2.86%)	4 / 72 (5.56%)	
occurrences causally related to treatment / all	2 / 2	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	4 / 70 (5.71%)	6 / 72 (8.33%)	
occurrences causally related to treatment / all	4 / 5	5 / 6	
deaths causally related to treatment / all	0 / 0	1 / 1	
Fever			
subjects affected / exposed	17 / 70 (24.29%)	18 / 72 (25.00%)	
occurrences causally related to treatment / all	18 / 30	10 / 28	
deaths causally related to treatment / all	0 / 1	0 / 4	
Flu like symptoms			
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothermia			
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pain			
subjects affected / exposed	2 / 70 (2.86%)	3 / 72 (4.17%)	
occurrences causally related to treatment / all	1 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 70 (5.71%)	5 / 72 (6.94%)	
occurrences causally related to treatment / all	2 / 4	4 / 5	
deaths causally related to treatment / all	0 / 0	1 / 1	
Dyspnea			
subjects affected / exposed	8 / 70 (11.43%)	14 / 72 (19.44%)	
occurrences causally related to treatment / all	3 / 8	12 / 19	
deaths causally related to treatment / all	0 / 2	2 / 3	
Pleuritic pain			
subjects affected / exposed	0 / 70 (0.00%)	2 / 72 (2.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Productive cough			
subjects affected / exposed	2 / 70 (2.86%)	2 / 72 (2.78%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders - Other			
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusion			
subjects affected / exposed	5 / 70 (7.14%)	2 / 72 (2.78%)	
occurrences causally related to treatment / all	2 / 5	1 / 2	
deaths causally related to treatment / all	1 / 2	0 / 0	
Anxiety			

subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Agitation			
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Investigations			
Blood bilirubin increased			
subjects affected / exposed	2 / 70 (2.86%)	4 / 72 (5.56%)	
occurrences causally related to treatment / all	2 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 2	
Creatinine increased			
subjects affected / exposed	1 / 70 (1.43%)	3 / 72 (4.17%)	
occurrences causally related to treatment / all	0 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
ECG QT corrected interval prolonged			
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INR increased			
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations - Other, specify			
subjects affected / exposed	0 / 70 (0.00%)	4 / 72 (5.56%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neutrophil count decreased			
subjects affected / exposed	5 / 70 (7.14%)	4 / 72 (5.56%)	
occurrences causally related to treatment / all	5 / 5	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			

subjects affected / exposed	2 / 70 (2.86%)	3 / 72 (4.17%)	
occurrences causally related to treatment / all	2 / 2	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell decreased			
subjects affected / exposed	1 / 70 (1.43%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphocyte count decreased			
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alkaline phosphatase increased			
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Chest pain - cardiac			
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Sinus tachycardia			
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (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			
Dizziness			
subjects affected / exposed	1 / 70 (1.43%)	3 / 72 (4.17%)	
occurrences causally related to treatment / all	1 / 2	3 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Headache			
subjects affected / exposed	2 / 70 (2.86%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	1 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischemia cerebrovascular			
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy			
subjects affected / exposed	0 / 70 (0.00%)	5 / 72 (6.94%)	
occurrences causally related to treatment / all	0 / 0	1 / 6	
deaths causally related to treatment / all	0 / 0	1 / 3	
Movements involuntary			
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Stroke			
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Syncope			
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders - Other,			

specify			
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (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			
Anemia			
subjects affected / exposed	3 / 70 (4.29%)	5 / 72 (6.94%)	
occurrences causally related to treatment / all	2 / 3	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 70 (1.43%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	10 / 70 (14.29%)	4 / 72 (5.56%)	
occurrences causally related to treatment / all	6 / 12	1 / 5	
deaths causally related to treatment / all	0 / 1	0 / 2	
Ascites			
subjects affected / exposed	1 / 70 (1.43%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	2 / 70 (2.86%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	4 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhea			
subjects affected / exposed	3 / 70 (4.29%)	9 / 72 (12.50%)	
occurrences causally related to treatment / all	3 / 4	7 / 12	
deaths causally related to treatment / all	0 / 0	0 / 1	

Nausea			
subjects affected / exposed	11 / 70 (15.71%)	3 / 72 (4.17%)	
occurrences causally related to treatment / all	9 / 15	2 / 3	
deaths causally related to treatment / all	0 / 2	0 / 0	
Vomiting			
subjects affected / exposed	16 / 70 (22.86%)	5 / 72 (6.94%)	
occurrences causally related to treatment / all	12 / 23	2 / 7	
deaths causally related to treatment / all	1 / 3	0 / 3	
Mucositis oral			
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bloating			
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dental caries			
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders - Other			
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bile duct stenosis			
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			

Erythema multiforme			
subjects affected / exposed	1 / 70 (1.43%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	1 / 70 (1.43%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders - Other			
subjects affected / exposed	0 / 70 (0.00%)	2 / 72 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Skin ulceration			
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain of skin			
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal and urinary disorders - Other, specify			
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary frequency			
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Urine discoloration			
subjects affected / exposed	1 / 70 (1.43%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Acute kidney injury			
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Chest wall pain			
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle weakness lower limb			
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infections and infestations			
Gum infection			
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations - Other			
subjects affected / exposed	2 / 70 (2.86%)	2 / 72 (2.78%)	
occurrences causally related to treatment / all	2 / 3	1 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung infection			
subjects affected / exposed	0 / 70 (0.00%)	2 / 72 (2.78%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Sepsis			
subjects affected / exposed	1 / 70 (1.43%)	3 / 72 (4.17%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	3 / 70 (4.29%)	4 / 72 (5.56%)	
occurrences causally related to treatment / all	1 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal infection			
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary tract infection			
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory infection			
subjects affected / exposed	2 / 70 (2.86%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	2 / 70 (2.86%)	2 / 72 (2.78%)	
occurrences causally related to treatment / all	2 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dehydration			

subjects affected / exposed	3 / 70 (4.29%)	2 / 72 (2.78%)	
occurrences causally related to treatment / all	2 / 3	1 / 2	
deaths causally related to treatment / all	1 / 1	0 / 0	
Hyperglycemia			
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatremia			
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (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	Arm A: Placebo plus Gemcitabine	Arm B: Vandetanib plus Gemcitabine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	64 / 70 (91.43%)	66 / 72 (91.67%)	
Vascular disorders			
FLUSHING			
subjects affected / exposed	1 / 70 (1.43%)	1 / 72 (1.39%)	
occurrences (all)	1	1	
HEMATOMA			
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	1	
HOT FLASHES			
subjects affected / exposed	1 / 70 (1.43%)	2 / 72 (2.78%)	
occurrences (all)	1	2	
HYPERTENSION			
subjects affected / exposed	11 / 70 (15.71%)	12 / 72 (16.67%)	
occurrences (all)	77	103	
HYPOTENSION			
subjects affected / exposed	3 / 70 (4.29%)	5 / 72 (6.94%)	
occurrences (all)	15	8	
PERIPHERAL ISCHEMIA			

subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)	
occurrences (all)	1	0	
PHLEBITIS			
subjects affected / exposed	2 / 70 (2.86%)	1 / 72 (1.39%)	
occurrences (all)	2	1	
SUPERFICIAL THROMBOPHLEBITIS			
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)	
occurrences (all)	1	0	
THROMBOEMBOLIC EVENT			
subjects affected / exposed	2 / 70 (2.86%)	4 / 72 (5.56%)	
occurrences (all)	3	6	
VASCULAR DISORDERS - OTHER, SPECIFY			
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
CHILLS			
subjects affected / exposed	4 / 70 (5.71%)	8 / 72 (11.11%)	
occurrences (all)	5	13	
EDEMA FACE			
subjects affected / exposed	1 / 70 (1.43%)	4 / 72 (5.56%)	
occurrences (all)	1	4	
EDEMA LIMBS			
subjects affected / exposed	9 / 70 (12.86%)	10 / 72 (13.89%)	
occurrences (all)	28	42	
EDEMA TRUNK			
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	1	
FATIGUE			
subjects affected / exposed	59 / 70 (84.29%)	66 / 72 (91.67%)	
occurrences (all)	603	628	
FEVER			
subjects affected / exposed	7 / 70 (10.00%)	8 / 72 (11.11%)	
occurrences (all)	13	14	
FLU LIKE SYMPTOMS			

subjects affected / exposed	6 / 70 (8.57%)	5 / 72 (6.94%)	
occurrences (all)	8	7	
GAIT DISTURBANCE			
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	1	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - OTHER, SPECIFY			
subjects affected / exposed	2 / 70 (2.86%)	3 / 72 (4.17%)	
occurrences (all)	2	4	
HYPOTHERMIA			
subjects affected / exposed	1 / 70 (1.43%)	1 / 72 (1.39%)	
occurrences (all)	1	1	
LOCALIZED EDEMA			
subjects affected / exposed	1 / 70 (1.43%)	1 / 72 (1.39%)	
occurrences (all)	2	1	
NON-CARDIAC CHEST PAIN			
subjects affected / exposed	1 / 70 (1.43%)	1 / 72 (1.39%)	
occurrences (all)	1	1	
PAIN			
subjects affected / exposed	5 / 70 (7.14%)	7 / 72 (9.72%)	
occurrences (all)	11	31	
Reproductive system and breast disorders			
BREAST PAIN			
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)	
occurrences (all)	1	0	
PENILE PAIN			
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)	
occurrences (all)	1	0	
PROSTATIC PAIN			
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)	
occurrences (all)	1	0	
VAGINAL DISCHARGE			
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	1	
VAGINAL DRYNESS			

subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	1	
VAGINAL HEMORRHAGE			
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
ASPIRATION			
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	1	
COUGH			
subjects affected / exposed	6 / 70 (8.57%)	8 / 72 (11.11%)	
occurrences (all)	12	14	
DYSPNEA			
subjects affected / exposed	9 / 70 (12.86%)	10 / 72 (13.89%)	
occurrences (all)	40	27	
EPISTAXIS			
subjects affected / exposed	3 / 70 (4.29%)	5 / 72 (6.94%)	
occurrences (all)	4	5	
HICCUPS			
subjects affected / exposed	0 / 70 (0.00%)	2 / 72 (2.78%)	
occurrences (all)	0	2	
HOARSENESS			
subjects affected / exposed	2 / 70 (2.86%)	1 / 72 (1.39%)	
occurrences (all)	2	1	
HYPOXIA			
subjects affected / exposed	1 / 70 (1.43%)	1 / 72 (1.39%)	
occurrences (all)	1	1	
LARYNGEAL INFLAMMATION			
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)	
occurrences (all)	1	0	
PLEURAL EFFUSION			
subjects affected / exposed	2 / 70 (2.86%)	3 / 72 (4.17%)	
occurrences (all)	2	3	
PLEURITIC PAIN			

subjects affected / exposed	0 / 70 (0.00%)	2 / 72 (2.78%)	
occurrences (all)	0	6	
PNEUMONITIS			
subjects affected / exposed	0 / 70 (0.00%)	2 / 72 (2.78%)	
occurrences (all)	0	3	
POSTNASAL DRIP			
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	2	
PULMONARY EDEMA			
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	1	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - OTHER, SPECIFY			
subjects affected / exposed	1 / 70 (1.43%)	2 / 72 (2.78%)	
occurrences (all)	1	2	
SINUS DISORDER			
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)	
occurrences (all)	1	0	
SORE THROAT			
subjects affected / exposed	3 / 70 (4.29%)	2 / 72 (2.78%)	
occurrences (all)	6	3	
VOICE ALTERATION			
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	1	
WHEEZING			
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
AGITATION			
subjects affected / exposed	1 / 70 (1.43%)	1 / 72 (1.39%)	
occurrences (all)	1	1	
ANXIETY			
subjects affected / exposed	3 / 70 (4.29%)	5 / 72 (6.94%)	
occurrences (all)	5	6	
CONFUSION			

subjects affected / exposed	1 / 70 (1.43%)	2 / 72 (2.78%)	
occurrences (all)	1	2	
DEPRESSION			
subjects affected / exposed	3 / 70 (4.29%)	6 / 72 (8.33%)	
occurrences (all)	3	13	
HALLUCINATIONS			
subjects affected / exposed	3 / 70 (4.29%)	0 / 72 (0.00%)	
occurrences (all)	7	0	
INSOMNIA			
subjects affected / exposed	3 / 70 (4.29%)	6 / 72 (8.33%)	
occurrences (all)	9	10	
LIBIDO DECREASED			
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	3	
PSYCHIATRIC DISORDERS - OTHER, SPECIFY			
subjects affected / exposed	1 / 70 (1.43%)	1 / 72 (1.39%)	
occurrences (all)	1	1	
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	52 / 70 (74.29%)	63 / 72 (87.50%)	
occurrences (all)	333	357	
ALKALINE PHOSPHATASE INCREASED			
subjects affected / exposed	47 / 70 (67.14%)	61 / 72 (84.72%)	
occurrences (all)	300	471	
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	44 / 70 (62.86%)	54 / 72 (75.00%)	
occurrences (all)	240	254	
BLOOD BILIRUBIN INCREASED			
subjects affected / exposed	15 / 70 (21.43%)	14 / 72 (19.44%)	
occurrences (all)	34	22	
CREATININE INCREASED			
subjects affected / exposed	12 / 70 (17.14%)	24 / 72 (33.33%)	
occurrences (all)	60	142	
ELECTROCARDIOGRAM QT CORRECTED INTERVAL PROLONGED			

subjects affected / exposed	2 / 70 (2.86%)	23 / 72 (31.94%)	
occurrences (all)	2	48	
GGT INCREASED			
subjects affected / exposed	53 / 70 (75.71%)	59 / 72 (81.94%)	
occurrences (all)	567	587	
INVESTIGATIONS - OTHER, SPECIFY			
subjects affected / exposed	45 / 70 (64.29%)	46 / 72 (63.89%)	
occurrences (all)	330	353	
LYMPHOCYTE COUNT DECREASED			
subjects affected / exposed	35 / 70 (50.00%)	40 / 72 (55.56%)	
occurrences (all)	321	164	
LYMPHOCYTE COUNT INCREASED			
subjects affected / exposed	1 / 70 (1.43%)	2 / 72 (2.78%)	
occurrences (all)	2	3	
NEUTROPHIL COUNT DECREASED			
subjects affected / exposed	42 / 70 (60.00%)	51 / 72 (70.83%)	
occurrences (all)	259	273	
PANCREATIC ENZYMES DECREASED			
subjects affected / exposed	3 / 70 (4.29%)	1 / 72 (1.39%)	
occurrences (all)	4	1	
PLATELET COUNT DECREASED			
subjects affected / exposed	47 / 70 (67.14%)	62 / 72 (86.11%)	
occurrences (all)	212	307	
WEIGHT LOSS			
subjects affected / exposed	3 / 70 (4.29%)	2 / 72 (2.78%)	
occurrences (all)	4	4	
WHITE BLOOD CELL DECREASED			
subjects affected / exposed	38 / 70 (54.29%)	50 / 72 (69.44%)	
occurrences (all)	307	225	
Injury, poisoning and procedural complications			
BRUISING			
subjects affected / exposed	2 / 70 (2.86%)	2 / 72 (2.78%)	
occurrences (all)	3	2	
FALL			

subjects affected / exposed	0 / 70 (0.00%)	2 / 72 (2.78%)	
occurrences (all)	0	3	
WOUND COMPLICATION			
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	1	
Cardiac disorders			
ACUTE CORONARY SYNDROME			
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	1	
ATRIAL FIBRILLATION			
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)	
occurrences (all)	1	0	
CARDIAC DISORDERS - OTHER, SPECIFY			
subjects affected / exposed	4 / 70 (5.71%)	3 / 72 (4.17%)	
occurrences (all)	9	10	
CHEST PAIN - CARDIAC			
subjects affected / exposed	2 / 70 (2.86%)	3 / 72 (4.17%)	
occurrences (all)	2	3	
LEFT VENTRICULAR SYSTOLIC DYSFUNCTION			
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	1	
PALPITATIONS			
subjects affected / exposed	1 / 70 (1.43%)	1 / 72 (1.39%)	
occurrences (all)	1	3	
SINUS BRADYCARDIA			
subjects affected / exposed	1 / 70 (1.43%)	2 / 72 (2.78%)	
occurrences (all)	1	4	
SINUS TACHYCARDIA			
subjects affected / exposed	2 / 70 (2.86%)	2 / 72 (2.78%)	
occurrences (all)	3	6	
Nervous system disorders			
COGNITIVE DISTURBANCE			
subjects affected / exposed	0 / 70 (0.00%)	2 / 72 (2.78%)	
occurrences (all)	0	2	
DEPRESSED LEVEL OF CONSCIOUSNESS			

subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)		
occurrences (all)	0	1		
DIZZINESS				
subjects affected / exposed	5 / 70 (7.14%)	7 / 72 (9.72%)		
occurrences (all)	23	14		
DYSGEUSIA				
subjects affected / exposed	3 / 70 (4.29%)	8 / 72 (11.11%)		
occurrences (all)	6	14		
ENCEPHALOPATHY				
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)		
occurrences (all)	0	1		
FACIAL MUSCLE WEAKNESS				
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)		
occurrences (all)	1	0		
HEADACHE				
subjects affected / exposed	5 / 70 (7.14%)	5 / 72 (6.94%)		
occurrences (all)	14	14		
LETHARGY				
subjects affected / exposed	42 / 70 (60.00%)	55 / 72 (76.39%)		
occurrences (all)	288	323		
MOVEMENTS INVOLUNTARY				
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)		
occurrences (all)	1	0		
NERVOUS SYSTEM DISORDERS - OTHER, SPECIFY				
subjects affected / exposed	1 / 70 (1.43%)	1 / 72 (1.39%)		
occurrences (all)	1	1		
NEURALGIA				
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)		
occurrences (all)	2	0		
PARESTHESIA				
subjects affected / exposed	1 / 70 (1.43%)	1 / 72 (1.39%)		
occurrences (all)	1	1		
PERIPHERAL MOTOR NEUROPATHY				
subjects affected / exposed	1 / 70 (1.43%)	4 / 72 (5.56%)		
occurrences (all)	1	5		

PERIPHERAL SENSORY NEUROPATHY			
subjects affected / exposed	1 / 70 (1.43%)	3 / 72 (4.17%)	
occurrences (all)	1	5	
SOMNOLENCE			
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)	
occurrences (all)	1	0	
SYNCOPE			
subjects affected / exposed	1 / 70 (1.43%)	2 / 72 (2.78%)	
occurrences (all)	2	2	
TREMOR			
subjects affected / exposed	2 / 70 (2.86%)	3 / 72 (4.17%)	
occurrences (all)	2	6	
VASOVAGAL REACTION			
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
ANEMIA			
subjects affected / exposed	64 / 70 (91.43%)	63 / 72 (87.50%)	
occurrences (all)	758	636	
BLOOD AND LYMPHATIC SYSTEM DISORDERS - OTHER, SPECIFY			
subjects affected / exposed	0 / 70 (0.00%)	2 / 72 (2.78%)	
occurrences (all)	0	7	
HEMOLYTIC UREMIC SYNDROME			
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)	
occurrences (all)	1	0	
LEUKOCYTOSIS			
subjects affected / exposed	11 / 70 (15.71%)	15 / 72 (20.83%)	
occurrences (all)	24	46	
THROMBOTIC THROMBOCYTOPENIC PURPURA			
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
EAR AND LABYRINTH DISORDERS - OTHER, SPECIFY			
subjects affected / exposed	1 / 70 (1.43%)	1 / 72 (1.39%)	
occurrences (all)	1	2	

TINNITUS			
subjects affected / exposed	2 / 70 (2.86%)	1 / 72 (1.39%)	
occurrences (all)	2	1	
VERTIGO			
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
BLURRED VISION			
subjects affected / exposed	1 / 70 (1.43%)	2 / 72 (2.78%)	
occurrences (all)	1	4	
EYE DISORDERS - OTHER, SPECIFY			
subjects affected / exposed	2 / 70 (2.86%)	3 / 72 (4.17%)	
occurrences (all)	3	4	
Gastrointestinal disorders			
ABDOMINAL DISTENSION			
subjects affected / exposed	2 / 70 (2.86%)	2 / 72 (2.78%)	
occurrences (all)	3	2	
ABDOMINAL PAIN			
subjects affected / exposed	56 / 70 (80.00%)	64 / 72 (88.89%)	
occurrences (all)	315	348	
ANAL PAIN			
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)	
occurrences (all)	1	0	
ASCITES			
subjects affected / exposed	4 / 70 (5.71%)	3 / 72 (4.17%)	
occurrences (all)	4	9	
BLOATING			
subjects affected / exposed	3 / 70 (4.29%)	5 / 72 (6.94%)	
occurrences (all)	4	7	
COLITIS			
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)	
occurrences (all)	1	0	
CONSTIPATION			
subjects affected / exposed	32 / 70 (45.71%)	40 / 72 (55.56%)	
occurrences (all)	121	133	
DENTAL CARIES			

subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)		
occurrences (all)	2	0		
DIARRHEA				
subjects affected / exposed	34 / 70 (48.57%)	54 / 72 (75.00%)		
occurrences (all)	176	373		
DRY MOUTH				
subjects affected / exposed	4 / 70 (5.71%)	9 / 72 (12.50%)		
occurrences (all)	6	13		
DYSPEPSIA				
subjects affected / exposed	3 / 70 (4.29%)	3 / 72 (4.17%)		
occurrences (all)	3	5		
DYSPHAGIA				
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)		
occurrences (all)	1	0		
FLATULENCE				
subjects affected / exposed	2 / 70 (2.86%)	4 / 72 (5.56%)		
occurrences (all)	3	4		
GASTRITIS				
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)		
occurrences (all)	1	0		
GASTROESOPHAGEAL REFLUX DISEASE				
subjects affected / exposed	2 / 70 (2.86%)	2 / 72 (2.78%)		
occurrences (all)	4	2		
GASTROINTESTINAL DISORDERS - OTHER, SPECIFY				
subjects affected / exposed	4 / 70 (5.71%)	5 / 72 (6.94%)		
occurrences (all)	7	6		
GASTROINTESTINAL PAIN				
subjects affected / exposed	1 / 70 (1.43%)	1 / 72 (1.39%)		
occurrences (all)	1	1		
HEMORRHOIDS				
subjects affected / exposed	1 / 70 (1.43%)	1 / 72 (1.39%)		
occurrences (all)	1	1		
LIP PAIN				

subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)	
occurrences (all)	1	0	
MALABSORPTION			
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)	
occurrences (all)	1	0	
MUCOSITIS ORAL			
subjects affected / exposed	27 / 70 (38.57%)	23 / 72 (31.94%)	
occurrences (all)	55	55	
NAUSEA			
subjects affected / exposed	49 / 70 (70.00%)	53 / 72 (73.61%)	
occurrences (all)	301	243	
OBSTRUCTION GASTRIC			
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)	
occurrences (all)	1	0	
ORAL PAIN			
subjects affected / exposed	0 / 70 (0.00%)	3 / 72 (4.17%)	
occurrences (all)	0	3	
PERIODONTAL DISEASE			
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	1	
RECTAL HEMORRHAGE			
subjects affected / exposed	1 / 70 (1.43%)	2 / 72 (2.78%)	
occurrences (all)	1	2	
TOOTHACHE			
subjects affected / exposed	1 / 70 (1.43%)	1 / 72 (1.39%)	
occurrences (all)	1	1	
VOMITING			
subjects affected / exposed	39 / 70 (55.71%)	33 / 72 (45.83%)	
occurrences (all)	112	72	
Hepatobiliary disorders			
BILE DUCT STENOSIS			
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
ALOPECIA			

subjects affected / exposed	5 / 70 (7.14%)	5 / 72 (6.94%)	
occurrences (all)	6	7	
DRY SKIN			
subjects affected / exposed	4 / 70 (5.71%)	5 / 72 (6.94%)	
occurrences (all)	4	9	
ERYTHEMA MULTIFORME			
subjects affected / exposed	1 / 70 (1.43%)	3 / 72 (4.17%)	
occurrences (all)	1	3	
ERYTHRODERMA			
subjects affected / exposed	1 / 70 (1.43%)	1 / 72 (1.39%)	
occurrences (all)	1	2	
HYPERHIDROSIS			
subjects affected / exposed	3 / 70 (4.29%)	0 / 72 (0.00%)	
occurrences (all)	3	0	
PALMAR-PLANTAR ERYTHRODYSESTHESIA SYNDROME			
subjects affected / exposed	0 / 70 (0.00%)	2 / 72 (2.78%)	
occurrences (all)	0	3	
PHOTOSENSITIVITY			
subjects affected / exposed	0 / 70 (0.00%)	2 / 72 (2.78%)	
occurrences (all)	0	2	
PRURITUS			
subjects affected / exposed	2 / 70 (2.86%)	3 / 72 (4.17%)	
occurrences (all)	3	3	
PURPURA			
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	1	
RASH ACNEIFORM			
subjects affected / exposed	1 / 70 (1.43%)	2 / 72 (2.78%)	
occurrences (all)	1	2	
RASH GENERALIZED			
subjects affected / exposed	1 / 70 (1.43%)	2 / 72 (2.78%)	
occurrences (all)	2	2	
RASH MACULO-PAPULAR			
subjects affected / exposed	20 / 70 (28.57%)	48 / 72 (66.67%)	
occurrences (all)	87	249	

SCALP PAIN			
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)	
occurrences (all)	1	0	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - OTHER, SPECIFY			
subjects affected / exposed	8 / 70 (11.43%)	4 / 72 (5.56%)	
occurrences (all)	17	12	
SKIN HYPERPIGMENTATION			
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	1	
SKIN HYPOPIGMENTATION			
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	1	
SKIN ULCERATION			
subjects affected / exposed	0 / 70 (0.00%)	3 / 72 (4.17%)	
occurrences (all)	0	3	
SURGICAL AND MEDICAL PROCEDURES - OTHER			
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
CHRONIC KIDNEY DISEASE			
subjects affected / exposed	9 / 70 (12.86%)	20 / 72 (27.78%)	
occurrences (all)	25	72	
HEMATURIA			
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	2	
PROTEINURIA			
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	1	
RENAL AND URINARY DISORDERS - OTHER, SPECIFY			
subjects affected / exposed	2 / 70 (2.86%)	2 / 72 (2.78%)	
occurrences (all)	2	2	
URINARY FREQUENCY			
subjects affected / exposed	3 / 70 (4.29%)	0 / 72 (0.00%)	
occurrences (all)	3	0	
URINARY INCONTINENCE			

subjects affected / exposed	0 / 70 (0.00%)	2 / 72 (2.78%)	
occurrences (all)	0	2	
URINARY URGENCY			
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	1	
URINE DISCOLORATION			
subjects affected / exposed	0 / 70 (0.00%)	2 / 72 (2.78%)	
occurrences (all)	0	2	
Endocrine disorders			
HYPERTHYROIDISM			
subjects affected / exposed	1 / 70 (1.43%)	1 / 72 (1.39%)	
occurrences (all)	1	1	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)	
occurrences (all)	1	0	
ARTHRITIS			
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)	
occurrences (all)	1	0	
BACK PAIN			
subjects affected / exposed	9 / 70 (12.86%)	9 / 72 (12.50%)	
occurrences (all)	14	19	
CHEST WALL PAIN			
subjects affected / exposed	2 / 70 (2.86%)	3 / 72 (4.17%)	
occurrences (all)	5	3	
FLANK PAIN			
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	1	
GENERALIZED MUSCLE WEAKNESS			
subjects affected / exposed	1 / 70 (1.43%)	2 / 72 (2.78%)	
occurrences (all)	1	3	
JOINT RANGE OF MOTION DECREASED			
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	1	
MUSCLE WEAKNESS LEFT-SIDED			

subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)	
occurrences (all)	1	0	
MUSCLE WEAKNESS LOWER LIMB			
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	1	
MUSCLE WEAKNESS TRUNK			
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	1	
MUSCLE WEAKNESS UPPER LIMB			
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)	
occurrences (all)	1	0	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDER - OTHER, SPECIFY			
subjects affected / exposed	2 / 70 (2.86%)	1 / 72 (1.39%)	
occurrences (all)	2	3	
MYALGIA			
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	1	
NECK PAIN			
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	1	
PAIN IN EXTREMITY			
subjects affected / exposed	4 / 70 (5.71%)	2 / 72 (2.78%)	
occurrences (all)	5	6	
Infections and infestations			
BILIARY TRACT INFECTION			
subjects affected / exposed	0 / 70 (0.00%)	3 / 72 (4.17%)	
occurrences (all)	0	3	
BLADDER INFECTION			
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	1	
BRONCHIAL INFECTION			
subjects affected / exposed	3 / 70 (4.29%)	2 / 72 (2.78%)	
occurrences (all)	8	2	
CORNEAL INFECTION			

subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)		
occurrences (all)	0	1		
GUM INFECTION				
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)		
occurrences (all)	1	0		
INFECTIONS AND INFESTATIONS - OTHER, SPECIFY				
subjects affected / exposed	3 / 70 (4.29%)	8 / 72 (11.11%)		
occurrences (all)	9	16		
LARYNGITIS				
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)		
occurrences (all)	0	1		
LIP INFECTION				
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)		
occurrences (all)	0	1		
LUNG INFECTION				
subjects affected / exposed	0 / 70 (0.00%)	3 / 72 (4.17%)		
occurrences (all)	0	3		
MEDIASTINAL INFECTION				
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)		
occurrences (all)	0	1		
PAPULOPUSTULAR RASH				
subjects affected / exposed	9 / 70 (12.86%)	22 / 72 (30.56%)		
occurrences (all)	30	82		
PENILE INFECTION				
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)		
occurrences (all)	1	0		
SKIN INFECTION				
subjects affected / exposed	2 / 70 (2.86%)	1 / 72 (1.39%)		
occurrences (all)	2	2		
TOOTH INFECTION				
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)		
occurrences (all)	0	1		
UPPER RESPIRATORY INFECTION				
subjects affected / exposed	3 / 70 (4.29%)	2 / 72 (2.78%)		
occurrences (all)	3	3		

URINARY TRACT INFECTION			
subjects affected / exposed	2 / 70 (2.86%)	4 / 72 (5.56%)	
occurrences (all)	10	5	
VAGINAL INFECTION			
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)	
occurrences (all)	2	0	
WOUND INFECTION			
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
ACIDOSIS			
subjects affected / exposed	1 / 70 (1.43%)	1 / 72 (1.39%)	
occurrences (all)	1	1	
ANOREXIA			
subjects affected / exposed	50 / 70 (71.43%)	59 / 72 (81.94%)	
occurrences (all)	202	241	
DEHYDRATION			
subjects affected / exposed	1 / 70 (1.43%)	1 / 72 (1.39%)	
occurrences (all)	1	1	
HYPERGLYCEMIA			
subjects affected / exposed	4 / 70 (5.71%)	3 / 72 (4.17%)	
occurrences (all)	5	5	
HYPERKALEMIA			
subjects affected / exposed	10 / 70 (14.29%)	12 / 72 (16.67%)	
occurrences (all)	18	20	
HYPERMAGNESEMIA			
subjects affected / exposed	3 / 70 (4.29%)	6 / 72 (8.33%)	
occurrences (all)	5	6	
HYPERNATREMIA			
subjects affected / exposed	0 / 70 (0.00%)	4 / 72 (5.56%)	
occurrences (all)	0	11	
HYPOALBUMINEMIA			
subjects affected / exposed	37 / 70 (52.86%)	49 / 72 (68.06%)	
occurrences (all)	228	275	
HYPOCALCEMIA			

subjects affected / exposed	20 / 70 (28.57%)	42 / 72 (58.33%)	
occurrences (all)	51	153	
HYPOGLYCEMIA			
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	2	
HYPOKALEMIA			
subjects affected / exposed	12 / 70 (17.14%)	15 / 72 (20.83%)	
occurrences (all)	23	28	
HYPOMAGNESEMIA			
subjects affected / exposed	11 / 70 (15.71%)	26 / 72 (36.11%)	
occurrences (all)	56	83	
HYPONATREMIA			
subjects affected / exposed	24 / 70 (34.29%)	35 / 72 (48.61%)	
occurrences (all)	93	140	
HYPOPHOSPHATEMIA			
subjects affected / exposed	1 / 70 (1.43%)	1 / 72 (1.39%)	
occurrences (all)	1	1	
METABOLISM AND NUTRITION DISORDERS - OTHER, SPECIFY			
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 February 2012	Protocol Version 5 (13/DEC/2012). Concomitant Medications/Treatments: Updated to include new guidance from version 14 of the Investigator Brochure describing interactions between vandetanib and metformin, as well as vandetanib and digoxin. Visit Schedule: The visit schedule was updated to stipulate that the medical review and physical examination completed for screening can be used for baseline if within 3 days of day 1 (start of treatment). Appendix C: Tables listing drugs considered to be associated with causing torsades de pointes (Tdp) were updated to reflect the list of drugs on the Arizona CERT website. A statement was also added that investigators need to periodically check the website for the most up to date drugs linked to causing Tdp. Additional information was added to table A (drugs with a high risk of causing Tdp) to clarify that none of the drugs listed in this table are to be taken 2 weeks prior to randomisation or during study treatment. Advice in table B and C was also updated with information on additional ECG and electrolyte monitoring that should be conducted if patients are taking drugs listed whilst on study treatment.
13 December 2013	Protocol version 6 (26/APR/2013). Main changes from version 5: Date: 13/Dec/2013 The sample size number has been updated throughout the protocol to reflect the additional 20 patients to be recruited, bringing the total to 140. The statistical section has also been updated explaining the reason for the additional patients being added is due to the importance of collecting quality translational samples for the development of a companion diagnostic test. This amendment will be implemented at research sites once regulatory approvals have been received.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported