



Clinical trial results:

Randomized Phase 2 Study of MLN8237, an Aurora A Kinase Inhibitor, Plus Weekly Paclitaxel or Weekly Paclitaxel Alone in Patients with Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer, Preceded by a Phase 1 Portion in Patients with Ovarian or Breast Cancer

Summary

EudraCT number	2009-011428-79
Trial protocol	PL
Global end of trial date	19 July 2017

Results information

Result version number	v1 (current)
This version publication date	11 March 2018
First version publication date	11 March 2018

Trial information

Trial identification

Sponsor protocol code	C14008
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01091428
WHO universal trial number (UTN)	U1111-1191-6584

Notes:

Sponsors

Sponsor organisation name	Takeda
Sponsor organisation address	40 Landsdowne Street, Cambridge, MA, United States, 02139
Public contact	Medical Director, Clinical Science, Takeda, +1 877-825-3327, trialdisclosures@takeda.com
Scientific contact	Medical Director, Clinical Science, Takeda, +1 877-825-3327, trialdisclosures@takeda.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 July 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 August 2014
Global end of trial reached?	Yes
Global end of trial date	19 July 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial is to evaluate MLN8237 in combination with weekly paclitaxel in adult female subjects with advanced breast cancer (Phase 1 portion only) and recurrent ovarian cancer (both Phase 1 and Phase 2 portions).

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 April 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 142
Country: Number of subjects enrolled	France: 31
Country: Number of subjects enrolled	Poland: 18
Worldwide total number of subjects	191
EEA total number of subjects	49

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)	131
From 65 to 84 years	60
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects took part in the study at 33 investigative sites in France, Poland and the United States from 16 April 2010 to 19 July 2017. Data cutoff for the primary analysis was 12 August 2014.

Pre-assignment

Screening details:

Subjects with a diagnosis of ovarian cancer or breast cancer were enrolled equally in a dose escalation study to determine the recommended Phase 2 dose. In Phase 2 subjects were randomized equally to receive alisertib 40 mg BID + paclitaxel 60 mg/m² or single-agent paclitaxel 80 mg/m².

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Alisertib (Phase 1 - Ovarian Cancer)

Arm description:

Subjects with ovarian cancer received alisertib (MLN8237) 10, 20, 30 or 40 mg, orally, twice daily (BID) on Days 1-3, 8-10 and 15-17, combined with weekly paclitaxel 60 or 80 mg/m², intravenous infusion, weekly (Days 1, 8, 15) in 28-day cycles in Phase 1 (Up to 37 cycles).

Arm type	Experimental
Investigational medicinal product name	Alisertib
Investigational medicinal product code	
Other name	MLN8237
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Alisertib Tablets

Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Paclitaxel Intravenous Infusion

Arm title	Alisertib (Phase 1 - Breast Cancer)
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Arm description:

Subjects with breast cancer received alisertib (MLN8237) 10, 20, 30 or 40 mg, orally, twice daily (BID) on Days 1-3, 8-10 and 15-17, combined with weekly paclitaxel 60 or 80 mg/m², intravenous infusion, weekly (Days 1, 8, 15) in 28-day cycles in Phase 1 (Up to 37 cycles).

Arm type	Experimental
Investigational medicinal product name	Alisertib
Investigational medicinal product code	
Other name	MLN8237
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:	
Alisertib Tablets	
Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Paclitaxel Intravenous Infusion	
Arm title	Alisertib 40 mg BID+ Paclitaxel 60 mg/m ² (Phase 2)
Arm description:	
Alisertib 40 mg, orally, BID on Days 1-3, 8-10 and 15-17, combined with weekly paclitaxel 60 mg/m ² , intravenous infusion, weekly (Days 1, 8, 15) in 28-day cycles in Phase 2 (Up to 28 cycles).	
Arm type	Experimental
Investigational medicinal product name	Alisertib
Investigational medicinal product code	
Other name	MLN8237
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Alisertib Tablets	
Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Paclitaxel intravenous Infusion	
Arm title	Paclitaxel 80 mg/m ² (Phase 2)
Arm description:	
Paclitaxel 80 mg/m ² , intravenous infusion, weekly (Days 1, 8, 15) in 28-day cycles in Phase 2 (Up to 28 cycles).	
Arm type	Experimental
Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Paclitaxel Intravenous Infusion	

Number of subjects in period 1	Alisertib (Phase 1 - Ovarian Cancer)	Alisertib (Phase 1 - Breast Cancer)	Alisertib 40 mg BID+ Paclitaxel 60 mg/m ² (Phase 2)
Started	38	11	73
Completed	0	0	0
Not completed	38	11	73
Unsatisfactory Therapeutic Response	-	-	1

Consent withdrawn by subject	7	-	9
Single-Patient IND	2	-	-
Physician Decision	-	-	2
Adverse event, non-fatal	2	-	12
Progressive Disease	24	8	44
Symptomatic Deterioration	3	2	1
Reason not specified	-	1	4

Number of subjects in period 1	Paclitaxel 80 mg/m² (Phase 2)
Started	69
Completed	0
Not completed	69
Unsatisfactory Therapeutic Response	1
Consent withdrawn by subject	8
Single-Patient IND	-
Physician Decision	-
Adverse event, non-fatal	5
Progressive Disease	46
Symptomatic Deterioration	6
Reason not specified	3

Baseline characteristics

Reporting groups

Reporting group title	Alisertib (Phase 1 - Ovarian Cancer)
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Reporting group description:

Subjects with ovarian cancer received alisertib (MLN8237) 10, 20, 30 or 40 mg, orally, twice daily (BID) on Days 1-3, 8-10 and 15-17, combined with weekly paclitaxel 60 or 80 mg/m², intravenous infusion, weekly (Days 1, 8, 15) in 28-day cycles in Phase 1 (Up to 37 cycles).

Reporting group title	Alisertib (Phase 1 - Breast Cancer)
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Reporting group description:

Subjects with breast cancer received alisertib (MLN8237) 10, 20, 30 or 40 mg, orally, twice daily (BID) on Days 1-3, 8-10 and 15-17, combined with weekly paclitaxel 60 or 80 mg/m², intravenous infusion, weekly (Days 1, 8, 15) in 28-day cycles in Phase 1 (Up to 37 cycles).

Reporting group title	Alisertib 40 mg BID+ Paclitaxel 60 mg/m ² (Phase 2)
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Reporting group description:

Alisertib 40 mg, orally, BID on Days 1-3, 8-10 and 15-17, combined with weekly paclitaxel 60 mg/m², intravenous infusion, weekly (Days 1, 8, 15) in 28-day cycles in Phase 2 (Up to 28 cycles).

Reporting group title	Paclitaxel 80 mg/m ² (Phase 2)
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Reporting group description:

Paclitaxel 80 mg/m², intravenous infusion, weekly (Days 1, 8, 15) in 28-day cycles in Phase 2 (Up to 28 cycles).

Reporting group values	Alisertib (Phase 1 - Ovarian Cancer)	Alisertib (Phase 1 - Breast Cancer)	Alisertib 40 mg BID+ Paclitaxel 60 mg/m ² (Phase 2)
Number of subjects	38	11	73
Age categorical Units: Subjects			

Age Continuous Units: years arithmetic mean standard deviation	55.8 ± 10.29	58.6 ± 10.06	61.0 ± 11.60
Gender, Male/Female Units: Subjects			
Female	38	11	73
Male	0	0	0
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino	4	0	1
Not Hispanic or Latino	34	10	64
Not Reported	0	1	7
Missing	0	0	1
Race/Ethnicity, Customized Units: Subjects			
White	34	11	66
Black or African American	3	0	2
Asian	1	0	1
American Indian or Alaskan Native	0	0	0
Other	0	0	1
Not Reported	0	0	2

Missing	0	0	1
Region of Enrollment Units: Subjects			
United States	38	11	48
Poland	0	0	10
France	0	0	15
Height Units: cm			
arithmetic mean	164.2	164.5	162.4
standard deviation	± 6.41	± 6.38	± 7.02
Weight Units: kg			
arithmetic mean	75.86	76.29	70.42
standard deviation	± 16.41	± 7.29	± 14.78
Body Surface Area			
Body Surface Area (m ²) = square root [height (cm) x weight (kg) / 3600].			
Units: m ²			
arithmetic mean	1.850	1.865	1.776
standard deviation	± 0.21	± 0.10	± 0.20

Reporting group values	Paclitaxel 80 mg/m ² (Phase 2)	Total	
Number of subjects	69	191	
Age categorical Units: Subjects			

Age Continuous Units: years			
arithmetic mean	60.8		
standard deviation	± 8.41	-	
Gender, Male/Female Units: Subjects			
Female	69	191	
Male	0	0	
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino	4	9	
Not Hispanic or Latino	62	170	
Not Reported	3	11	
Missing	0	1	
Race/Ethnicity, Customized Units: Subjects			
White	55	166	
Black or African American	6	11	
Asian	2	4	
American Indian or Alaskan Native	2	2	
Other	1	2	
Not Reported	3	5	
Missing	0	1	
Region of Enrollment Units: Subjects			
United States	45	142	

Poland	8	18	
France	16	31	

Height			
Units: cm			
arithmetic mean	161.9		
standard deviation	± 7.30	-	
Weight			
Units: kg			
arithmetic mean	72.50		
standard deviation	± 18.71	-	
Body Surface Area			
Body Surface Area (m ²) = square root [height (cm) x weight (kg) / 3600].			
Units: m ²			
arithmetic mean	1.794		
standard deviation	± 0.24	-	

End points

End points reporting groups

Reporting group title	Alisertib (Phase 1 - Ovarian Cancer)
Reporting group description: Subjects with ovarian cancer received alisertib (MLN8237) 10, 20, 30 or 40 mg, orally, twice daily (BID) on Days 1-3, 8-10 and 15-17, combined with weekly paclitaxel 60 or 80 mg/m ² , intravenous infusion, weekly (Days 1, 8, 15) in 28-day cycles in Phase 1 (Up to 37 cycles).	
Reporting group title	Alisertib (Phase 1 - Breast Cancer)
Reporting group description: Subjects with breast cancer received alisertib (MLN8237) 10, 20, 30 or 40 mg, orally, twice daily (BID) on Days 1-3, 8-10 and 15-17, combined with weekly paclitaxel 60 or 80 mg/m ² , intravenous infusion, weekly (Days 1, 8, 15) in 28-day cycles in Phase 1 (Up to 37 cycles).	
Reporting group title	Alisertib 40 mg BID+ Paclitaxel 60 mg/m ² (Phase 2)
Reporting group description: Alisertib 40 mg, orally, BID on Days 1-3, 8-10 and 15-17, combined with weekly paclitaxel 60 mg/m ² , intravenous infusion, weekly (Days 1, 8, 15) in 28-day cycles in Phase 2 (Up to 28 cycles).	
Reporting group title	Paclitaxel 80 mg/m ² (Phase 2)
Reporting group description: Paclitaxel 80 mg/m ² , intravenous infusion, weekly (Days 1, 8, 15) in 28-day cycles in Phase 2 (Up to 28 cycles).	
Subject analysis set title	Alisertib + Paclitaxel (Phase 1)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects with ovarian cancer received alisertib (MLN8237) 10, 20, 30 or 40 mg, orally, twice daily (BID) on Days 1-3, 8-10 and 15-17, combined with weekly paclitaxel 60 or 80 mg/m ² , intravenous infusion, weekly (Days 1, 8, 15) in 28-day cycles in Phase 1 (Up to 37 cycles).	
Subject analysis set title	Alisertib + Paclitaxel
Subject analysis set type	Sub-group analysis
Subject analysis set description: Paclitaxel 60 or 80 mg/m ² , intravenous infusion, weekly (Days 1, 8, 15) in 28-day cycles in Phase 1.	
Subject analysis set title	Alisertib 10 mg BID + Paclitaxel 80 mg/m ²
Subject analysis set type	Sub-group analysis
Subject analysis set description: Alisertib (MLN8237) 10 mg, orally, twice daily (BID) on Days 1-3, 8-10 and 15-17, combined with weekly paclitaxel 80 mg/m ² , intravenous infusion, weekly (Days 1, 8, 15) in 28-day cycles in Phase 1.	
Subject analysis set title	Alisertib 20 mg BID + Paclitaxel 80 mg/m ²
Subject analysis set type	Sub-group analysis
Subject analysis set description: Alisertib 20 mg, orally, twice daily (BID) on Days 1-3, 8-10 and 15-17, combined with weekly paclitaxel 80 mg/m ² , intravenous infusion, weekly (Days 1, 8, 15) in 28-day cycles in Phase 1.	
Subject analysis set title	Alisertib 20 mg BID + Paclitaxel 60 mg/m ²
Subject analysis set type	Sub-group analysis
Subject analysis set description: Alisertib 20 mg, orally, twice daily (BID) on Days 1-3, 8-10 and 15-17, combined with weekly paclitaxel 60 mg/m ² , intravenous infusion, weekly (Days 1, 8, 15) in 28-day cycles in Phase 1.	
Subject analysis set title	Alisertib 30 mg BID + Paclitaxel 60 mg/m ²
Subject analysis set type	Sub-group analysis
Subject analysis set description: Alisertib 30 mg, orally, twice daily (BID) on Days 1-3, 8-10 and 15-17, combined with weekly paclitaxel 60 mg/m ² , intravenous infusion, weekly (Days 1, 8, 15) in 28-day cycles in Phase 1.	
Subject analysis set title	Alisertib 40 mg BID + Paclitaxel 60 mg/m ²
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Alisertib 10 mg, orally, twice daily (BID) on Days 1-3, 8-10 and 15-17, combined with weekly paclitaxel 80 mg/m², intravenous infusion, weekly (Days 1, 8, 15) in 28-day cycles in Phase 1.

Subject analysis set title	Alisertib 50 mg BID + Paclitaxel 60 mg/m ²
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Alisertib 10 mg, orally, twice daily (BID) on Days 1-3, 8-10 and 15-17, combined with weekly paclitaxel 80 mg/m², intravenous infusion, weekly (Days 1, 8, 15) in 28-day cycles in Phase 1

Subject analysis set title	Alisertib 40 mg BID + Paclitaxel 60 mg/m ² (Phase 2)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Alisertib 40 mg, orally, BID on Days 1-3, 8-10 and 15-17, combined with weekly paclitaxel 60 mg/m², intravenous infusion, weekly (Days 1, 8, 15) in 28-day cycles in Phase 2 (Up to 28 cycles).

Primary: Phase 1: Maximum Tolerated Dose (MTD) and Recommended Phase 2 Dose (RP2D) for Alisertib in Combination with Paclitaxel

End point title	Phase 1: Maximum Tolerated Dose (MTD) and Recommended Phase 2 Dose (RP2D) for Alisertib in Combination with Paclitaxel ^[1]
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End point description:

MTD: Dose range at which ≤ 1 of 6 evaluable subjects experience dose limiting toxicities (DLT). DLT evaluated a/c to National Cancer Institute's Common Terminology Criteria for Adverse v4.02 & as any of events: 1. Grade 4 neutropenia & thrombocytopenia lasting ≥ 7 consecutive days; 2. Grade 4 neutropenia with fever/infection; 3. Platelet count $< 10,000/\text{mm}^3$; 4. Grade 3 thrombocytopenia with bleeding; 5. Any other \geq Grade 3 nonhematologic toxicity, with exceptions: \geq Grade 3 nausea/emesis, \geq Grade 3 diarrhoea, Grade 3 fatigue, Grade 3 nonhematological toxicity that is controlled to \leq Grade 2 with appropriate treatment; 6. Other alisertib-related nonhematologic toxicities \geq Grade 2 that, in investigator opinion, required a dose reduction/discontinuation of therapy with alisertib. DLT-Evaluable Population: all subjects in phase 1 who experienced DLT during Cycle 1/completed treatment with 15 of planned 18 doses of alisertib & 2 of planned 3 doses of paclitaxel in Cycle 1 & had sufficient follow-up data.

End point type	Primary
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End point timeframe:

Cycle 1 (Up to 28 days)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses are reported for this endpoint.

End point values	Alisertib + Paclitaxel (Phase 1)			
Subject group type	Subject analysis set			
Number of subjects analysed	49			
Units: mg	40			

Statistical analyses

No statistical analyses for this end point

Primary: Phase 1: MTD and RP2D for Paclitaxel in Combination with Alisertib

End point title	Phase 1: MTD and RP2D for Paclitaxel in Combination with Alisertib ^[2]
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End point description:

The RP2D is the maximum tolerated dose (MTD) or less. The MTD is defined as the dose range at which ≤ 1 of 6 evaluable subjects experience dose limiting toxicities (DLT) within the first 28 days of treatment

(end of cycle 1). DLT-Evaluable Population was defined as all subjects in the phase 1 who either experienced DLT during Cycle 1 or completed treatment with at least 15 of the planned 18 doses of alisertib and 2 of the planned 3 doses of paclitaxel in Cycle 1 and had sufficient follow-up data.

End point type	Primary
End point timeframe:	
Cycle 1 (Up to 28 days)	

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses are reported for this endpoint.

End point values	Alisertib + Paclitaxel			
Subject group type	Subject analysis set			
Number of subjects analysed	49			
Units: mg/m ²	60			

Statistical analyses

No statistical analyses for this end point

Primary: Phase 1: Number of Subjects with Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Phase 1: Number of Subjects with Adverse Events (AEs) and Serious Adverse Events (SAEs) ^{[3][4]}
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End point description:

An Adverse Event (AE) is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment. A Serious Adverse Event (SAE) A serious is any experience that suggests a significant hazard, contraindication, side effect or precaution that results in death, is life-threatening, required in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect or is medically significant. Safety population was defined as all subjects who received at least 1 dose of any study drug.

End point type	Primary
End point timeframe:	
First dose to 30 days past last dose (Up to 36 Months)	

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses are reported for this endpoint.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Not all arms in the Baseline Period are applicable to this Endpoint.

End point values	Alisertib (Phase 1 - Ovarian Cancer)	Alisertib (Phase 1 - Breast Cancer)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	11		
Units: subjects				
AEs	38	11		
SAEs	13	2		

Statistical analyses

No statistical analyses for this end point

Primary: Phase 1: Number of Subjects with Clinically Significant Laboratory Values

End point title	Phase 1: Number of Subjects with Clinically Significant Laboratory Values ^{[5][6]}
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End point description:

Abnormal clinical laboratory values (serum chemistry, hematology and urinalysis) were reported as AEs if they were considered by the investigator to be a clinically significant change from Baseline or led to premature discontinuation of study treatment, dose modification, or other therapeutic intervention. Safety population was defined as all subjects who received at least 1 dose of any study drug.

End point type	Primary
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End point timeframe:

First dose to 30 days past last dose (Up to 36 Months)

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses are reported for this endpoint.

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Not all arms in the Baseline Period are applicable to this Endpoint.

End point values	Alisertib (Phase 1 - Ovarian Cancer)	Alisertib (Phase 1 - Breast Cancer)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	11		
Units: subjects				
Neutrophil count decreased	3	0		
White blood cell count decreased	1	1		
Aspartate aminotransferase increased	3	1		
Alanine aminotransferase increased	2	0		
Ammonia increased	1	0		
Transaminases increased	1	0		
Blood alkaline phosphatase increased	1	1		
High density lipoprotein decreased	1	0		
Urine output decreased	1	0		
Granulocyte count decreased	0	1		

Statistical analyses

No statistical analyses for this end point

Primary: Phase 1: Number of Subjects with Clinically Significant Vital Sign Findings

End point title	Phase 1: Number of Subjects with Clinically Significant Vital Sign Findings ^[7] ^[8]
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End point description:

Vital signs (blood pressure, pulse rate, and oral temperature) measurements were collected throughout the study. Safety population was defined as all subjects who received at least 1 dose of any study drug.

End point type	Primary
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End point timeframe:

First dose to 30 days past last dose (Up to 36 Months)

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses are reported for this endpoint.

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Not all arms in the Baseline Period are applicable to this Endpoint.

End point values	Alisertib (Phase 1 - Ovarian Cancer)	Alisertib (Phase 1 - Breast Cancer)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	11		
Units: subjects				
Pyrexia	8	5		
Heart rate irregular	1	0		
Blood pressure increased	0	1		
Weight decreased	3	0		

Statistical analyses

No statistical analyses for this end point

Primary: Phase 1: Number of Subjects with Hypersensitivity and Neurotoxicity

End point title	Phase 1: Number of Subjects with Hypersensitivity and Neurotoxicity ^[9] ^[10]
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End point description:

Safety population was defined as all subjects who received at least 1 dose of any study drug.

End point type	Primary
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End point timeframe:

Baseline up to Month 36

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses are reported for this endpoint.

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Not all arms in the Baseline Period are applicable to this Endpoint.

End point values	Alisertib (Phase 1 - Ovarian Cancer)	Alisertib (Phase 1 - Breast Cancer)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	11		
Units: subjects				
Hypersensitivity	1	0		
Neurotoxicity	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Phase 2: Progression-Free Survival (PFS)

End point title	Phase 2: Progression-Free Survival (PFS) ^{[11][12]}
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End point description:

PFS is defined as the time from the date randomization for Phase 2 subjects to the date of first documented progressive disease (PD) or death as assessed by the investigator using both RECIST 1.1 criteria and CA-125 criteria. PD is defined as 20% increase in the sum of the longest diameter of target lesions for measurable neoplastic disease or CA-125 criteria with elevated (>70 units/mL) levels on 2 occasions. CA 125 progression for subjects with normal CA 125 levels is defined as a CA 125 level >2 times the upper limit of normal and for subjects with elevated values during the trial, is defined as a CA 125 level greater than 2 times the nadir value of CA 125. The modified intent-to-treat (mITT) population was defined as all subjects who were randomized and received at least 1 dose of any study drug. For a subject that has not progressed and has not died or has started the alternate therapy, PFS is censored at the last response assessment that is stable disease (SD) or better.

End point type	Primary
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End point timeframe:

At the end of Cycle 2 and at the completion of every 2 cycles until PD was documented or up to data cut-off: 12 August 2014 (approximately 24 months)

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses are reported for this endpoint.

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Not all arms in the Baseline Period are applicable to this Endpoint.

End point values	Alisertib 40 mg BID+ Paclitaxel 60 mg/m ² (Phase 2)	Paclitaxel 80 mg/m ² (Phase 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	69		
Units: days				
median (confidence interval 80%)	204 (175 to 230)	142 (117 to 148)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: Combined Best Overall Response Rate (ORR) in Subjects with Recurrent Ovarian Cancer or Breast Cancer

End point title	Phase 1: Combined Best Overall Response Rate (ORR) in Subjects with Recurrent Ovarian Cancer or Breast Cancer ^[13]
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End point description:

Combined objective response rate: Percentage of subjects with Complete Response (CR)+Partial Response (PR) as assessed by investigator according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria 1.1 or response by Cancer antigen (CA) 125 criteria. According to RECIST: CR- disappearance of all target lesions & PR- 30% decrease in sum of longest diameter of target lesions. CA-125 response criteria: 50% decrease from 2 initially elevated samples; sample demonstrating 50% decrease must be confirmed by a fourth sample 28 days later (total of 4 samples required) or serial decrease of >75% over 3 samples; third sample was obtained 28 days after second (total of 3 samples required). Response evaluable population: Subjects who were randomized & had measurable disease according to RECIST or assessable disease by CA-125 criteria, who received at least 1 dose of any study drug & who had at least 1 available post-Baseline response assessment as per either RECIST or CA-125 criteria.

End point type	Secondary
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End point timeframe:

At the end of Cycle 2 and at the completion of every 2 cycles until PD was documented or up to data cut-off: 12 August 2014 (approximately 24 months)

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Not all arms in the Baseline Period are applicable to this Endpoint.

End point values	Alisertib (Phase 1 - Ovarian Cancer)	Alisertib (Phase 1 - Breast Cancer)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	11		
Units: percentage of subjects				
number (confidence interval 80%)	47 (36 to 59)	55 (32 to 76)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax: Maximum Observed Concentration for Alisertib in Phase 1

End point title	Cmax: Maximum Observed Concentration for Alisertib in Phase 1
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End point description:

Pharmacokinetic (PK) analysis set for alisertib was defined as all subjects in the phase 1 portion of the study for whom there was sufficient dosing and alisertib concentration-time data to permit noncompartmental PK analysis.

End point type	Secondary
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End point timeframe:

Days 1 and 3 in Cycle 1: pre-dose and at multiple timepoints (up to 12 hours) post morning dose

End point values	Alisertib 10 mg BID + Paclitaxel 80 mg/m ²	Alisertib 20 mg BID + Paclitaxel 80 mg/m ²	Alisertib 20 mg BID + Paclitaxel 60 mg/m ²	Alisertib 30 mg BID + Paclitaxel 60 mg/m ²
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	15	6	4	6
Units: nM				
arithmetic mean (standard deviation)				
Cycle1 (Day1)	428.7 (± 189.59)	766.8 (± 312.10)	900.00 (± 392.17)	1365.3 (± 466.51)
Cycle1 (Day3)	594.3 (± 228.46)	1042.3 (± 280.95)	871.3 (± 268.23)	1708.5 (± 820.54)

End point values	Alisertib 40 mg BID + Paclitaxel 60 mg/m ²	Alisertib 50 mg BID + Paclitaxel 60 mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	3		
Units: nM				
arithmetic mean (standard deviation)				
Cycle1 (Day1)	1398.7 (± 607.70)	1960.0 (± 515.65)		
Cycle1 (Day3)	2493.4 (± 955.31)	4456.7 (± 947.33)		

Statistical analyses

No statistical analyses for this end point

Secondary: Tmax: Time to First Occurrence of Cmax for Alisertib in Phase 1

End point title	Tmax: Time to First Occurrence of Cmax for Alisertib in Phase 1
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End point description:

PK analysis set for alisertib was defined as all subjects in the phase 1 portion of the study for whom there was sufficient dosing and alisertib concentration-time data to permit noncompartmental PK analysis.

End point type	Secondary
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End point timeframe:

Days 1 and 3 in Cycle 1: pre-dose and at multiple timepoints (up to 12 hours) post morning dose

End point values	Alisertib 10 mg BID + Paclitaxel 80 mg/m ²	Alisertib 20 mg BID + Paclitaxel 80 mg/m ²	Alisertib 20 mg BID + Paclitaxel 60 mg/m ²	Alisertib 30 mg BID + Paclitaxel 60 mg/m ²
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	15	6	4	6
Units: hour				
median (full range (min-max))				

Cycle 1, Day 1	3.0 (1 to 5)	3.1 (2 to 4)	2.6 (2 to 3)	2.5 (2 to 9)
Cycle 1, Day 3	2.2 (0 to 5)	3.0 (1 to 3)	3.5 (2 to 5)	2.0 (1 to 4)

End point values	Alisertib 40 mg BID + Paclitaxel 60 mg/m ²	Alisertib 50 mg BID + Paclitaxel 60 mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	3		
Units: hour				
median (full range (min-max))				
Cycle 1, Day 1	3.0 (2 to 9)	2.0 (2 to 9)		
Cycle 1, Day 3	2.0 (1 to 9)	2.0 (2 to 3)		

Statistical analyses

No statistical analyses for this end point

Secondary: AUC(tau): Area Under the Concentration-Time Curve During a Dosing Interval for Alisertib in Phase 1

End point title	AUC(tau): Area Under the Concentration-Time Curve During a Dosing Interval for Alisertib in Phase 1
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End point description:

PK analysis set for alisertib was defined as all subjects in the phase 1 portion of the study for whom there was sufficient dosing and alisertib concentration-time data to permit noncompartmental PK analysis.

End point type	Secondary
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End point timeframe:

Days 1 and 3 in Cycle 1: pre-dose and at multiple timepoints (up to 12 hours) post morning dose

End point values	Alisertib 10 mg BID + Paclitaxel 80 mg/m ²	Alisertib 20 mg BID + Paclitaxel 80 mg/m ²	Alisertib 20 mg BID + Paclitaxel 60 mg/m ²	Alisertib 30 mg BID + Paclitaxel 60 mg/m ²
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	15	6	4	6
Units: nM*hour				
arithmetic mean (standard deviation)				
Cycle 1, Day 1	2519.3 (± 937.52)	5175.0 (± 1766.11)	5610.0 (± 2105.42)	8581.7 (± 3225.64)
Cycle 1, Day3	3966.7 (± 1112.11)	7745.0 (± 2233.91)	6155.0 (± 1737.69)	12478.3 (± 6013.93)

End point values	Alisertib 40 mg BID +	Alisertib 50 mg BID +		
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	Paclitaxel 60 mg/m ²	Paclitaxel 60 mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	3		
Units: nM*hour				
arithmetic mean (standard deviation)				
Cycle 1, Day 1	9594.0 (± 4600.42)	14666.7 (± 3707.20)		
Cycle 1, Day3	17557.3 (± 7856.30)	35500.0 (± 12842.12)		

Statistical analyses

No statistical analyses for this end point

Secondary: AUClast: Area under the Concentration-Time Curve from Time 0 to the Time of the Last Quantifiable Concentration for Alisertib in Phase 1

End point title	AUClast: Area under the Concentration-Time Curve from Time 0 to the Time of the Last Quantifiable Concentration for Alisertib in Phase 1
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End point description:

PK analysis set for alisertib was defined as all subjects in the phase 1 portion of the study for whom there was sufficient dosing and alisertib concentration-time data to permit noncompartmental PK analysis.

End point type	Secondary
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End point timeframe:

Days 1 and 3 in Cycle 1: pre-dose and at multiple timepoints (up to 12 hours) post morning dose

End point values	Alisertib 10 mg BID + Paclitaxel 80 mg/m ²	Alisertib 20 mg BID + Paclitaxel 80 mg/m ²	Alisertib 20 mg BID + Paclitaxel 60 mg/m ²	Alisertib 30 mg BID + Paclitaxel 60 mg/m ²
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	15	6	4	6
Units: nM*hour				
arithmetic mean (standard deviation)				
Cycle 1, Day 1	2519.3 (± 937.52)	5175.0 (± 1766.11)	5610.0 (± 2105.42)	8581.7 (± 3225.64)
Cycle 1, Day 3	3966.7 (± 1112.11)	7745.0 (± 2233.91)	6155.0 (± 1737.69)	12478.3 (± 6013.93)

End point values	Alisertib 40 mg BID + Paclitaxel 60 mg/m ²	Alisertib 50 mg BID + Paclitaxel 60 mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	3		
Units: nM*hour				

arithmetic mean (standard deviation)				
Cycle 1, Day 1	9594.0 (± 4600.42)	14666.7 (± 3707.20)		
Cycle 1, Day 3	17557.3 (± 7856.30)	35500.0 (± 12842.12)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax: Maximum Observed Concentration for Paclitaxel in Phase 1

End point title	Cmax: Maximum Observed Concentration for Paclitaxel in Phase 1
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End point description:

PK analysis set for paclitaxel was defined as all subjects in the phase 1 portion of the study for whom there was sufficient dosing and paclitaxel concentration-time data to permit noncompartmental PK analysis. Number analyzed is the number of subjects with evaluable data at the specified time-point.

End point type	Secondary
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End point timeframe:

Day 1 in Cycles 1 and 2: pre-infusion and at multiple timepoints (up to 47 hours) post-infusion

End point values	Alisertib 10 mg BID + Paclitaxel 80 mg/m ²	Alisertib 20 mg BID + Paclitaxel 80 mg/m ²	Alisertib 20 mg BID + Paclitaxel 60 mg/m ²	Alisertib 30 mg BID + Paclitaxel 60 mg/m ²
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	15	6	4	6
Units: ng/mL*hr				
arithmetic mean (standard deviation)				
Cycle 1, Day 1 (n=15,6,4,5,15,3)	3097.3 (± 1114.51)	3120.0 (± 447.75)	2117.5 (± 745.54)	2448.0 (± 988.65)
Cycle 2, Day 1 (n=13,6,3,6,13,2)	2654.6 (± 696.45)	3231.7 (± 615.64)	1733.3 (± 541.97)	2478.3 (± 878.39)

End point values	Alisertib 40 mg BID + Paclitaxel 60 mg/m ²	Alisertib 50 mg BID + Paclitaxel 60 mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	3		
Units: ng/mL*hr				
arithmetic mean (standard deviation)				
Cycle 1, Day 1 (n=15,6,4,5,15,3)	1917.3 (± 528.32)	1338.7 (± 617.94)		
Cycle 2, Day 1 (n=13,6,3,6,13,2)	1492.7 (± 558.14)	1750.0 (± 183.85)		

Statistical analyses

No statistical analyses for this end point

Secondary: AUClast: Area under the Concentration-Time Curve from Time 0 to the Time of the Last Quantifiable Concentration for Paclitaxel in Phase 1

End point title	AUClast: Area under the Concentration-Time Curve from Time 0 to the Time of the Last Quantifiable Concentration for Paclitaxel in Phase 1
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End point description:

PK analysis set for paclitaxel was defined as all subjects in the phase 1 portion of the study for whom there was sufficient dosing and paclitaxel concentration-time data to permit noncompartmental PK analysis. Number analyzed is the number of subjects with evaluable data at the specified time-point.

End point type	Secondary
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End point timeframe:

Day 1 in Cycles 1 and 2: pre-infusion and at multiple timepoints (up to 47 hours) post-infusion

End point values	Alisertib 10 mg BID + Paclitaxel 80 mg/m ²	Alisertib 20 mg BID + Paclitaxel 80 mg/m ²	Alisertib 20 mg BID + Paclitaxel 60 mg/m ²	Alisertib 30 mg BID + Paclitaxel 60 mg/m ²
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	15	6	4	6
Units: ng/mL*hr				
arithmetic mean (standard deviation)				
Cycle 1, Day 1 (n=13,6,4,5,15,3)	4437.7 (± 1053.87)	4825.0 (± 735.17)	3355.0 (± 865.89)	3366.0 (± 1139.25)
Cycle 2, Day 1 (n=12,6,3,5,13,2)	4061.7 (± 1298.86)	5301.7 (± 1183.31)	2660.0 (± 307.90)	3056.0 (± 812.67)

End point values	Alisertib 40 mg BID + Paclitaxel 60 mg/m ²	Alisertib 50 mg BID + Paclitaxel 60 mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	3		
Units: ng/mL*hr				
arithmetic mean (standard deviation)				
Cycle 1, Day 1 (n=13,6,4,5,15,3)	2652.7 (± 651.32)	2190.0 (± 387.43)		
Cycle 2, Day 1 (n=12,6,3,5,13,2)	2231.5 (± 604.76)	2460.0 (± 14.14)		

Statistical analyses

No statistical analyses for this end point

Secondary: AUC0-∞: Area under the Concentration-Time Curve from Time 0 to Infinity, Calculated using the Observed Value of the Last Quantifiable Concentration for Paclitaxel in Phase 1

End point title	AUC0-∞: Area under the Concentration-Time Curve from Time 0 to Infinity, Calculated using the Observed Value of the Last Quantifiable Concentration for Paclitaxel in Phase 1
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End point description:

PK analysis set for paclitaxel was defined as all subjects in the phase 1 portion of the study for whom there was sufficient dosing and paclitaxel concentration-time data to permit noncompartmental PK analysis. Number analyzed is the number of subjects with evaluable data at the specified time-point. Here, 99999 indicates that data was not collected as no subject was evaluated at the specified time point.

End point type	Secondary
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End point timeframe:

Day 1 in Cycles 1 and 2: pre-infusion and at multiple timepoints (up to 47 hours) post-infusion

End point values	Alisertib 10 mg BID + Paclitaxel 80 mg/m ²	Alisertib 20 mg BID + Paclitaxel 80 mg/m ²	Alisertib 20 mg BID + Paclitaxel 60 mg/m ²	Alisertib 30 mg BID + Paclitaxel 60 mg/m ²
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	15	6	4	6
Units: ng/mL*hr				
arithmetic mean (standard deviation)				
Cycle 1, Day 1 (n=9,5,3,4,11,2)	5317.8 (± 1052.40)	5238.0 (± 812.26)	3860.0 (± 824.20)	3375.0 (± 1130.56)
Cycle 2, Day 1 (n=11,5,2,4,10,0)	4606.4 (± 1391.35)	5584.0 (± 1367.51)	3185.0 (± 176.78)	3415.0 (± 1010.82)

End point values	Alisertib 40 mg BID + Paclitaxel 60 mg/m ²	Alisertib 50 mg BID + Paclitaxel 60 mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	3		
Units: ng/mL*hr				
arithmetic mean (standard deviation)				
Cycle 1, Day 1 (n=9,5,3,4,11,2)	3175.5 (± 933.10)	2535.0 (± 657.61)		
Cycle 2, Day 1 (n=11,5,2,4,10,0)	2680.0 (± 607.22)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: t_{1/2}: Terminal Half-Life for Paclitaxel in Phase 1

End point title	t _{1/2} : Terminal Half-Life for Paclitaxel in Phase 1
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End point description:

PK analysis set for paclitaxel was defined as all subjects in the phase 1 portion of the study for whom there was sufficient dosing and paclitaxel concentration-time data to permit noncompartmental PK analysis. Number analyzed is the number of subjects with evaluable data at the specified time-point.

End point type	Secondary
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End point timeframe:

Day 1 in Cycles 1 and 2: pre-infusion and at multiple timepoints (up to 47 hours) post-infusion

End point values	Alisertib 10 mg BID + Paclitaxel 80 mg/m ²	Alisertib 20 mg BID + Paclitaxel 80 mg/m ²	Alisertib 20 mg BID + Paclitaxel 60 mg/m ²	Alisertib 30 mg BID + Paclitaxel 60 mg/m ²
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	15	6	4	6
Units: hour				
arithmetic mean (standard deviation)				
Cycle 1, Day 1 (n=11,5,3,5,11,2)	17.2 (± 4.20)	17.5 (± 1.87)	17.3 (± 4.16)	13.9 (± 4.68)
Cycle 2, Day 1 (n=12,5,2,4,10,2)	17.0 (± 3.63)	16.2 (± 5.05)	17.3 (± 5.23)	16.5 (± 4.32)

End point values	Alisertib 40 mg BID + Paclitaxel 60 mg/m ²	Alisertib 50 mg BID + Paclitaxel 60 mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	3		
Units: hour				
arithmetic mean (standard deviation)				
Cycle 1, Day 1 (n=11,5,3,5,11,2)	16.8 (± 6.83)	18.4 (± 8.70)		
Cycle 2, Day 1 (n=12,5,2,4,10,2)	13.3 (± 5.59)	14.6 (± 2.19)		

Statistical analyses

No statistical analyses for this end point

Secondary: CL: Total Clearance After Intravenous Administration, Calculated Using the Observed Value of the Last Quantifiable Concentration for Paclitaxel in Phase 1

End point title	CL: Total Clearance After Intravenous Administration, Calculated Using the Observed Value of the Last Quantifiable Concentration for Paclitaxel in Phase 1
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End point description:

PK analysis set for paclitaxel was defined as all subjects in the phase 1 portion of the study for whom there was sufficient dosing and paclitaxel concentration-time data to permit noncompartmental PK analysis. Number analyzed is the number of subjects with evaluable data at the specified time-point. Here, 99999 indicates that data was not collected as no subject was evaluated at the specified time point.

End point type	Secondary
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End point timeframe:

Day 1 in Cycles 1 and 2: pre-infusion and at multiple timepoints (up to 47 hours) post-infusion

End point values	Alisertib 10 mg BID + Paclitaxel 80 mg/m ²	Alisertib 20 mg BID + Paclitaxel 80 mg/m ²	Alisertib 20 mg BID + Paclitaxel 60 mg/m ²	Alisertib 30 mg BID + Paclitaxel 60 mg/m ²
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	15	6	4	6
Units: liter per hour				
arithmetic mean (standard deviation)				
Cycle 1, Day 1 (n=9,5,3,4,11,2)	29.756 (± 6.8175)	28.220 (± 5.1804)	26.800 (± 7.5386)	40.950 (± 17.5268)
Cycle 2, Day 1 (n=11,5,2,4,10,0)	35.827 (± 10.4005)	28.240 (± 7.3748)	33.900 (± 5.2326)	34.250 (± 8.2614)

End point values	Alisertib 40 mg BID + Paclitaxel 60 mg/m ²	Alisertib 50 mg BID + Paclitaxel 60 mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	3		
Units: liter per hour				
arithmetic mean (standard deviation)				
Cycle 1, Day 1 (n=9,5,3,4,11,2)	38.055 (± 13.7095)	38.950 (± 11.2430)		
Cycle 2, Day 1 (n=11,5,2,4,10,0)	42.440 (± 10.4296)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Vss: Volume of Distribution at Steady State for Paclitaxel in Phase 1

End point title	Vss: Volume of Distribution at Steady State for Paclitaxel in Phase 1
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End point description:

PK analysis set for paclitaxel was defined as all subjects in the phase 1 portion of the study for whom there was sufficient dosing and paclitaxel concentration-time data to permit noncompartmental PK analysis. Number analyzed is the number of subjects with evaluable data at the specified time-point. Here, 99999 indicates that data was not collected as no subject was evaluated at the specified time point.

End point type	Secondary
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End point timeframe:

Day 1 in Cycles 1 and 2: pre-infusion and at multiple timepoints (up to 47 hours) post-infusion

End point values	Alisertib 10 mg BID + Paclitaxel 80 mg/m ²	Alisertib 20 mg BID + Paclitaxel 80 mg/m ²	Alisertib 20 mg BID + Paclitaxel 60 mg/m ²	Alisertib 30 mg BID + Paclitaxel 60 mg/m ²
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	15	6	4	6
Units: liter				
arithmetic mean (standard deviation)				
Cycle 1, Day 1 (n=9,5,3,4,11,2)	313.444 (± 118.6593)	310.800 (± 86.9235)	330.000 (± 208.8851)	357.000 (± 158.1834)
Cycle 2, Day 1 (n=11,5,2,4,10,0)	391.364 (± 64.3137)	283.200 (± 121.1123)	413.500 (± 242.5376)	377.000 (± 118.9650)

End point values	Alisertib 40 mg BID + Paclitaxel 60 mg/m ²	Alisertib 50 mg BID + Paclitaxel 60 mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	3		
Units: liter				
arithmetic mean (standard deviation)				
Cycle 1, Day 1 (n=9,5,3,4,11,2)	433.909 (± 179.7757)	460.500 (± 103.9447)		
Cycle 2, Day 1 (n=11,5,2,4,10,0)	372.600 (± 180.7332)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Vz: Volume of Distribution During the Terminal Disposition Phase for Paclitaxel in Phase 1

End point title	Vz: Volume of Distribution During the Terminal Disposition Phase for Paclitaxel in Phase 1
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End point description:

PK analysis set for paclitaxel was defined as all subjects in the phase 1 portion of the study for whom there was sufficient dosing and paclitaxel concentration-time data to permit noncompartmental PK analysis. Number analyzed is the number of subjects with evaluable data at the specified time-point. Here, 99999 indicates that data was not collected as no subject was evaluated at the specified time

point.

End point type	Secondary
End point timeframe:	
Day 1 in Cycles 1 and 2: pre-infusion and at multiple timepoints (up to 47 hours) post-infusion	

End point values	Alisertib 10 mg BID + Paclitaxel 80 mg/m ²	Alisertib 20 mg BID + Paclitaxel 80 mg/m ²	Alisertib 20 mg BID + Paclitaxel 60 mg/m ²	Alisertib 30 mg BID + Paclitaxel 60 mg/m ²
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	15	6	4	6
Units: liter				
arithmetic mean (standard deviation)				
Cycle 1, Day 1 (n=9,5,3,4,11,2)	705.000 (± 179.0223)	721.600 (± 203.8021)	694.000 (± 352.1534)	850.500 (± 291.0401)
Cycle 2, Day 1 (n=11,5,2,4,10,0)	829.364 (± 156.6060)	663.200 (± 321.3070)	865.500 (± 388.2016)	777.250 (± 103.7027)

End point values	Alisertib 40 mg BID + Paclitaxel 60 mg/m ²	Alisertib 50 mg BID + Paclitaxel 60 mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	3		
Units: liter				
arithmetic mean (standard deviation)				
Cycle 1, Day 1 (n=9,5,3,4,11,2)	872.727 (± 328.6202)	956.500 (± 188.7975)		
Cycle 2, Day 1 (n=11,5,2,4,10,0)	733.000 (± 208.4898)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Combined Best Overall Response Rate (ORR)

End point title	Phase 2: Combined Best Overall Response Rate (ORR) ^[14]
End point description:	
Combined objective response rate: Percentage of subjects with CR+ PR as assessed by the investigator according to RECIST criteria 1.1 or response by CA-125 criteria. According to RECIST: CR- the disappearance of all target lesions and PR- 30% decrease in the sum of the longest diameter of target lesions. CA-125 response criteria is defined as either: A 50% decrease from 2 initially elevated samples; the sample demonstrating the 50% decrease must have been confirmed by a fourth sample 28 days later (a total of 4 samples required) or A serial decrease of >75% over 3 samples; the third sample was to be obtained 28 days after the second (a total of 3 samples required). Response evaluable population was defined as all subjects who were randomized and had measurable disease according to RECIST or assessable disease by CA-125 criteria, who received at least 1 dose of any study drug, and who had at least 1 available post-Baseline response assessment as per either RECIST or CA-125 criteria.	
End point type	Secondary

End point timeframe:

At the end of Cycle 2 and at the completion of every 2 cycles until PD was documented or up to data cut-off: 12 August 2014 (approximately 24 months)

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Not all arms in the Baseline Period are applicable to this Endpoint.

End point values	Alisertib 40 mg BID+ Paclitaxel 60 mg/m ² (Phase 2)	Paclitaxel 80 mg/m ² (Phase 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	64		
Units: percentage of subjects				
number (confidence interval 80%)	60 (51 to 68)	52 (43 to 60)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Duration of Response (DOR)

End point title	Phase 2: Duration of Response (DOR) ^[15]
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End point description:

DOR: Time from date of first documentation of response to date of first documentation of PD or last response assessment i.e. stable disease (SD) or better for subject who started alternate therapy without progression. PD: 20% increase in sum of longest diameter of target lesions for measurable neoplastic disease or per CA-125 criteria with elevated (>70 units/mL) levels on 2 occasions. CA-125 progression for subjects with normal CA-125 levels: CA-125 level >2 times upper limit of normal and for subjects with elevated values during trial: CA-125 level >2 times nadir value of CA-125. A responder that did not experience disease progression is censored at last response assessment i.e. SD. Response evaluable population: subjects who were randomized and had measurable disease according to RECIST 1.1 or assessable disease by CA-125 criteria, who received 1 dose of study drug, and who had 1 available post-Baseline response assessment per RECIST 1.1 or CA-125 criteria, who were responders.

End point type	Secondary
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End point timeframe:

Up to data-cut off: 12 August 2014 (approximately 24 months)

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Not all arms in the Baseline Period are applicable to this Endpoint.

End point values	Alisertib 40 mg BID+ Paclitaxel 60 mg/m ² (Phase 2)	Paclitaxel 80 mg/m ² (Phase 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	33		
Units: days				
median (confidence interval 80%)	201 (181 to 218)	169 (120 to 231)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Time to Disease Progression (TTP)

End point title	Phase 2: Time to Disease Progression (TTP) ^[16]
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End point description:

TTP was defined as the time from the date of randomization to the date of first documentation of PD. PD is defined as 20% increase in the sum of the longest diameter of target lesions for measurable neoplastic disease or per CA-125 criteria with elevated (>70 units/mL) levels on 2 occasions. CA 125 progression for subjects with normal CA 125 levels is defined as a CA 125 level >2 times the upper limit of normal and for subjects with elevated values during the trial, is defined as a CA 125 level greater than 2 times the nadir value of CA 125. mITT Population was defined as all subjects who were randomized and received at least 1 dose of any study drug. For a subject that has not progressed, TTP is censored at the last response assessment that is SD or better.

End point type	Secondary
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End point timeframe:

Up to data-cut off: 12 August 2014 (approximately 24 months)

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Not all arms in the Baseline Period are applicable to this Endpoint.

End point values	Alisertib 40 mg BID+ Paclitaxel 60 mg/m ² (Phase 2)	Paclitaxel 80 mg/m ² (Phase 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	69		
Units: days				
median (confidence interval 80%)	204 (175 to 232)	142 (117 to 161)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Overall Survival (OS)

End point title	Phase 2: Overall Survival (OS) ^[17]
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End point description:

OS was defined as the time from the date of the randomization to the date of death. mITT Population was defined as all subjects who were randomized and received at least 1 dose of any study drug. For a subject that is alive, OS will be censored at the last known date. Here, 99999 indicates that Median, upper and lower limits of CI were not reached due to low number of subjects with events.

End point type	Secondary
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End point timeframe:

Up to data-cut off: 12 August 2014 (approximately 24 months)

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Not all arms in the Baseline Period are applicable to this Endpoint.

End point values	Alisertib 40 mg BID+ Paclitaxel 60 mg/m ² (Phase 2)	Paclitaxel 80 mg/m ² (Phase 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	69		
Units: days				
median (confidence interval 80%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Number of Subjects with Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Phase 2: Number of Subjects with Adverse Events (AEs) and Serious Adverse Events (SAEs) ^[18]
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End point description:

An Adverse Event (AE) is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment. A Serious Adverse Event (SAE) A serious is any experience that suggests a significant hazard, contraindication, side effect or precaution that: results in death, is life-threatening, required in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect or is medically significant. Safety population was defined as all subjects who received at least 1 dose of any study drug.

End point type	Secondary
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End point timeframe:

First dose to 30 days past last dose (Up to 27 Months)

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Not all arms in the Baseline Period are applicable to this Endpoint.

End point values	Alisertib 40 mg BID+ Paclitaxel 60 mg/m ² (Phase 2)	Paclitaxel 80 mg/m ² (Phase 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	69		
Units: subjects				
AEs	73	66		
SAEs	30	19		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Number of Subjects With Clinically Significant Laboratory Values

End point title	Phase 2: Number of Subjects With Clinically Significant Laboratory Values ^[19]
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End point description:

Abnormal clinical laboratory values (serum chemistry, hematology, and urinalysis) were reported as AEs if they were considered by the investigator to be a clinically significant change from Baseline or led to premature discontinuation of study treatment, dose modification, or other therapeutic intervention. Safety population was defined as all subjects who received at least 1 dose of any study drug.

End point type	Secondary
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End point timeframe:

First dose to 30 days past last dose (Up to 27 Months)

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Not all arms in the Baseline Period are applicable to this Endpoint.

End point values	Paclitaxel 80 mg/m ² (Phase 2)	Alisertib 40 mg BID + Paclitaxel 60 mg/m ² (Phase 2)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	69	73		
Units: subjects				
Neutrophil count decreased	4	14		
White blood cell count decreased	1	6		
Lymphocyte count decreased	1	1		
Aspartate aminotransferase increased	3	1		
Alanine aminotransferase increased	4	1		
Gamma-glutamyltransferase increased	1	0		
Blood alkaline phosphatase increased	2	2		
Haemoglobin decreased	1	3		
Blood magnesium decreased	3	0		
Blood creatinine increased	2	1		
Platelet count decreased	0	2		
International normalised ratio increased	0	1		
Blood albumin decreased	0	1		
Troponin T increased	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Number of Subjects with Clinically Significant Vital Sign Findings

End point title	Phase 2: Number of Subjects with Clinically Significant Vital Sign Findings ^[20]
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End point description:

Vital signs (blood pressure, pulse rate, and oral temperature) measurements were collected throughout the study. Safety population was defined as all subjects who received at least 1 dose of any study drug.

End point type	Secondary
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End point timeframe:

First dose to 30 days past last dose (Up to 27 Months)

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Not all arms in the Baseline Period are applicable to this Endpoint.

End point values	Paclitaxel 80 mg/m ² (Phase 2)	Alisertib 40 mg BID + Paclitaxel 60 mg/m ² (Phase 2)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	69	73		
Units: Subjects				
Pyrexia	8	15		
Heart rate increased	0	1		
Blood pressure increased	0	1		
Weight decreased	2	8		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Banked Tumor Specimens for Candidate Markers of Response to Alisertib and Taxanes

End point title	Banked Tumor Specimens for Candidate Markers of Response to Alisertib and Taxanes
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End point description:

This Outcome Measure was originally registered as a Secondary but this Outcome Measure was Exploratory and no data was collected.

End point type	Other pre-specified
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End point timeframe:

Up to 24 Months

End point values	Alisertib + Paclitaxel (Phase 1)			
Subject group type	Subject analysis set			
Number of subjects analysed	0 ^[21]			
Units: levels				
arithmetic mean (standard deviation)	()			

Notes:

[21] - This endpoint was registered as a Secondary but this was Exploratory and no data was collected.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Phase 1: First dose to 30 days past last dose (Up to 36 Months); Phase 2: First dose to 30 days past last dose (Up to 27 Months)

Adverse event reporting additional description:

At each visit the investigator had to document any occurrence of adverse events and abnormal laboratory findings. Any event spontaneously reported by the subject or observed by the investigator was recorded, irrespective of the relation to study treatment.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.0
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Reporting groups

Reporting group title	Alisertib (Phase 1 - Ovarian cancer)
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Reporting group description:

Alisertib (MLN8237) 10 mg, orally, twice daily (BID) on Days 1-3, 8-10 and 15-17, combined with weekly paclitaxel 80 mg/m², intravenous infusion, weekly (Days 1, 8, 15) in 28-day cycles in Phase 1.

Reporting group title	Alisertib (Phase 1 - Breast cancer)
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Reporting group description:

Alisertib 20 mg, orally, twice daily (BID) on Days 1-3, 8-10 and 15-17, combined with weekly paclitaxel 80 mg/m², intravenous infusion, weekly (Days 1, 8, 15) in 28-day cycles in Phase 1.

Reporting group title	Alisertib 40 mg BID+ Paclitaxel 60 mg/m ² (Phase 2)
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Reporting group description:

Alisertib 40 mg, orally, BID on Days 1-3, 8-10 and 15-17, combined with weekly paclitaxel 60 mg/m², intravenous infusion, weekly (Days 1, 8, 15) in 28-day cycles in Phase 2 (Up to 28 cycles).

Reporting group title	Paclitaxel 80 mg/m ² (Phase 2)
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Reporting group description:

Paclitaxel 80 mg/m², intravenous infusion, weekly (Days 1, 8, 15) in 28-day cycles in Phase 2 (Up to 28 cycles).

Serious adverse events	Alisertib (Phase 1 - Ovarian cancer)	Alisertib (Phase 1 - Breast cancer)	Alisertib 40 mg BID+ Paclitaxel 60 mg/m ² (Phase 2)
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 38 (34.21%)	2 / 11 (18.18%)	30 / 73 (41.10%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant pleural effusion			
subjects affected / exposed	0 / 38 (0.00%)	0 / 11 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			

Deep vein thrombosis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 11 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Venous thrombosis limb			
subjects affected / exposed	0 / 38 (0.00%)	0 / 11 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	1 / 38 (2.63%)	1 / 11 (9.09%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolism			
subjects affected / exposed	0 / 38 (0.00%)	0 / 11 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 11 (9.09%)	3 / 73 (4.11%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	1 / 38 (2.63%)	0 / 11 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	1 / 38 (2.63%)	1 / 11 (9.09%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 38 (0.00%)	0 / 11 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 38 (0.00%)	1 / 11 (9.09%)	2 / 73 (2.74%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachypnoea			
subjects affected / exposed	1 / 38 (2.63%)	0 / 11 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary alveolar haemorrhage			
subjects affected / exposed	0 / 38 (0.00%)	0 / 11 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 38 (0.00%)	0 / 11 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 38 (0.00%)	0 / 11 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Neutrophil count decreased			
subjects affected / exposed	0 / 38 (0.00%)	0 / 11 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
White blood cell count decreased			
subjects affected / exposed	0 / 38 (0.00%)	0 / 11 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Troponin T increased			

subjects affected / exposed	0 / 38 (0.00%)	0 / 11 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Vascular access complication			
subjects affected / exposed	0 / 38 (0.00%)	0 / 11 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 38 (0.00%)	0 / 11 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pubis fracture			
subjects affected / exposed	0 / 38 (0.00%)	0 / 11 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 38 (0.00%)	0 / 11 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 38 (0.00%)	0 / 11 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	6 / 38 (15.79%)	0 / 11 (0.00%)	9 / 73 (12.33%)
occurrences causally related to treatment / all	6 / 9	0 / 0	9 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 38 (0.00%)	0 / 11 (0.00%)	6 / 73 (8.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	6 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Anaemia			
subjects affected / exposed	1 / 38 (2.63%)	0 / 11 (0.00%)	2 / 73 (2.74%)
occurrences causally related to treatment / all	0 / 1	0 / 0	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic anaemia			
subjects affected / exposed	0 / 38 (0.00%)	0 / 11 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Hearing impaired			
subjects affected / exposed	0 / 38 (0.00%)	0 / 11 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 38 (2.63%)	0 / 11 (0.00%)	3 / 73 (4.11%)
occurrences causally related to treatment / all	0 / 1	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 38 (2.63%)	0 / 11 (0.00%)	2 / 73 (2.74%)
occurrences causally related to treatment / all	0 / 1	0 / 0	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 38 (0.00%)	0 / 11 (0.00%)	4 / 73 (5.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	1 / 38 (2.63%)	0 / 11 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	2 / 38 (5.26%)	0 / 11 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Abdominal pain lower			
subjects affected / exposed	0 / 38 (0.00%)	0 / 11 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 38 (2.63%)	0 / 11 (0.00%)	2 / 73 (2.74%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction	Additional description: One treatment-emergent death occurred during treatment with alisertib and paclitaxel and was not related.		
subjects affected / exposed	0 / 38 (0.00%)	0 / 11 (0.00%)	2 / 73 (2.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Constipation			
subjects affected / exposed	0 / 38 (0.00%)	0 / 11 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 11 (0.00%)	2 / 73 (2.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal hernia obstructive			
subjects affected / exposed	0 / 38 (0.00%)	0 / 11 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proctalgia			
subjects affected / exposed	0 / 38 (0.00%)	0 / 11 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric perforation			
subjects affected / exposed	0 / 38 (0.00%)	0 / 11 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation			

subjects affected / exposed	0 / 38 (0.00%)	0 / 11 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 38 (0.00%)	0 / 11 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	0 / 38 (0.00%)	0 / 11 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic ascites			
subjects affected / exposed	1 / 38 (2.63%)	0 / 11 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	0 / 38 (0.00%)	0 / 11 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Paraneoplastic dermatomyositis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 11 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 38 (0.00%)	0 / 11 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postrenal failure			
subjects affected / exposed	1 / 38 (2.63%)	0 / 11 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Renal failure			
subjects affected / exposed	0 / 38 (0.00%)	0 / 11 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Flank pain			
subjects affected / exposed	1 / 38 (2.63%)	0 / 11 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Device related infection			
subjects affected / exposed	1 / 38 (2.63%)	0 / 11 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess soft tissue			
subjects affected / exposed	0 / 38 (0.00%)	0 / 11 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 38 (0.00%)	0 / 11 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 38 (0.00%)	0 / 11 (0.00%)	3 / 73 (4.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 11 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	2 / 38 (5.26%)	0 / 11 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pyelonephritis			
subjects affected / exposed	1 / 38 (2.63%)	0 / 11 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 38 (2.63%)	1 / 11 (9.09%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheter site cellulitis			
subjects affected / exposed	1 / 38 (2.63%)	0 / 11 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis	Additional description: One treatment-emergent death occurred during treatment with paclitaxel and was not related.		
subjects affected / exposed	0 / 38 (0.00%)	1 / 11 (9.09%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 38 (2.63%)	0 / 11 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile infection			
subjects affected / exposed	1 / 38 (2.63%)	0 / 11 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 38 (0.00%)	0 / 11 (0.00%)	4 / 73 (5.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	1 / 38 (2.63%)	0 / 11 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Paclitaxel 80 mg/m ² (Phase 2)		
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 69 (27.54%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant pleural effusion			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Venous thrombosis limb			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Embolism			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 69 (2.90%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Asthenia			

subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fatigue			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oedema peripheral			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Tachypnoea			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary alveolar haemorrhage			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Investigations			
Neutrophil count decreased			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
White blood cell count decreased			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Troponin T increased			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Vascular access complication			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pubis fracture			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Syncope			

subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Anaemia			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Haemorrhagic anaemia			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Hearing impaired			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 69 (2.90%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	2 / 69 (2.90%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Intestinal obstruction				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	0 / 69 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abdominal pain				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal pain lower				
subjects affected / exposed	0 / 69 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction	Additional description: One treatment-emergent death occurred during treatment with alisertib and paclitaxel and was not related.			
subjects affected / exposed	2 / 69 (2.90%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Stomatitis				
subjects affected / exposed	0 / 69 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abdominal hernia obstructive				

subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Proctalgia			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastric perforation			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intestinal perforation			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ascites			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemorrhagic ascites			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			

Paraneoplastic dermatomyositis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 69 (1.45%) 0 / 1 0 / 0		
Renal and urinary disorders Acute kidney injury subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 69 (1.45%) 0 / 1 0 / 0		
Postrenal failure subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 69 (0.00%) 0 / 0 0 / 0		
Renal failure subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 69 (1.45%) 0 / 1 0 / 0		
Musculoskeletal and connective tissue disorders Flank pain subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 69 (0.00%) 0 / 0 0 / 0		
Infections and infestations Device related infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all Abscess soft tissue subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all Infection	1 / 69 (1.45%) 0 / 1 0 / 0 0 / 69 (0.00%) 0 / 0 0 / 0		

subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Catheter site cellulitis			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sepsis	Additional description: One treatment-emergent death occurred during treatment with paclitaxel and was not related.		
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Gastroenteritis			

subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Clostridium difficile infection			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Alisertib (Phase 1 - Ovarian cancer)	Alisertib (Phase 1 - Breast cancer)	Alisertib 40 mg BID+ Paclitaxel 60 mg/m ² (Phase 2)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 38 (100.00%)	11 / 11 (100.00%)	73 / 73 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 38 (0.00%)	1 / 11 (9.09%)	0 / 73 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Flushing			
subjects affected / exposed	2 / 38 (5.26%)	1 / 11 (9.09%)	3 / 73 (4.11%)
occurrences (all)	2	1	5
Hot flush			
subjects affected / exposed	3 / 38 (7.89%)	0 / 11 (0.00%)	1 / 73 (1.37%)
occurrences (all)	4	0	1
Hypotension			

subjects affected / exposed	0 / 38 (0.00%)	0 / 11 (0.00%)	4 / 73 (5.48%)
occurrences (all)	0	0	5
Deep vein thrombosis			
subjects affected / exposed	1 / 38 (2.63%)	1 / 11 (9.09%)	1 / 73 (1.37%)
occurrences (all)	1	1	1
Lymphoedema			
subjects affected / exposed	1 / 38 (2.63%)	1 / 11 (9.09%)	1 / 73 (1.37%)
occurrences (all)	1	1	1
Orthostatic hypotension			
subjects affected / exposed	3 / 38 (7.89%)	0 / 11 (0.00%)	0 / 73 (0.00%)
occurrences (all)	3	0	0
Blood pressure fluctuation			
subjects affected / exposed	0 / 38 (0.00%)	1 / 11 (9.09%)	0 / 73 (0.00%)
occurrences (all)	0	1	0
Superior vena cava stenosis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 11 (9.09%)	0 / 73 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	26 / 38 (68.42%)	8 / 11 (72.73%)	43 / 73 (58.90%)
occurrences (all)	29	10	82
Oedema peripheral			
subjects affected / exposed	15 / 38 (39.47%)	3 / 11 (27.27%)	12 / 73 (16.44%)
occurrences (all)	24	3	15
Pyrexia			
subjects affected / exposed	8 / 38 (21.05%)	4 / 11 (36.36%)	13 / 73 (17.81%)
occurrences (all)	11	7	18
Asthenia			
subjects affected / exposed	5 / 38 (13.16%)	2 / 11 (18.18%)	10 / 73 (13.70%)
occurrences (all)	6	2	20
Chills			
subjects affected / exposed	10 / 38 (26.32%)	0 / 11 (0.00%)	6 / 73 (8.22%)
occurrences (all)	12	0	6
Non-cardiac chest pain			

subjects affected / exposed	2 / 38 (5.26%)	2 / 11 (18.18%)	3 / 73 (4.11%)
occurrences (all)	2	2	4
Catheter site pain			
subjects affected / exposed	3 / 38 (7.89%)	0 / 11 (0.00%)	2 / 73 (2.74%)
occurrences (all)	5	0	2
Peripheral swelling			
subjects affected / exposed	2 / 38 (5.26%)	0 / 11 (0.00%)	2 / 73 (2.74%)
occurrences (all)	3	0	4
Pain			
subjects affected / exposed	2 / 38 (5.26%)	0 / 11 (0.00%)	1 / 73 (1.37%)
occurrences (all)	2	0	1
Chest discomfort			
subjects affected / exposed	2 / 38 (5.26%)	0 / 11 (0.00%)	0 / 73 (0.00%)
occurrences (all)	2	0	0
Early satiety			
subjects affected / exposed	1 / 38 (2.63%)	1 / 11 (9.09%)	0 / 73 (0.00%)
occurrences (all)	1	1	0
Localised oedema			
subjects affected / exposed	0 / 38 (0.00%)	1 / 11 (9.09%)	0 / 73 (0.00%)
occurrences (all)	0	1	0
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	3 / 38 (7.89%)	1 / 11 (9.09%)	0 / 73 (0.00%)
occurrences (all)	3	1	0
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	3 / 38 (7.89%)	0 / 11 (0.00%)	0 / 73 (0.00%)
occurrences (all)	4	0	0
Genital discomfort			
subjects affected / exposed	1 / 38 (2.63%)	1 / 11 (9.09%)	1 / 73 (1.37%)
occurrences (all)	1	1	1
Vulvovaginal pain			
subjects affected / exposed	3 / 38 (7.89%)	0 / 11 (0.00%)	0 / 73 (0.00%)
occurrences (all)	3	0	0
Cystocele			

subjects affected / exposed	1 / 38 (2.63%)	1 / 11 (9.09%)	0 / 73 (0.00%)
occurrences (all)	1	1	0
Postmenopausal haemorrhage			
subjects affected / exposed	0 / 38 (0.00%)	1 / 11 (9.09%)	0 / 73 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	11 / 38 (28.95%)	3 / 11 (27.27%)	17 / 73 (23.29%)
occurrences (all)	13	3	20
Dyspnoea			
subjects affected / exposed	10 / 38 (26.32%)	3 / 11 (27.27%)	9 / 73 (12.33%)
occurrences (all)	11	3	10
Epistaxis			
subjects affected / exposed	7 / 38 (18.42%)	1 / 11 (9.09%)	6 / 73 (8.22%)
occurrences (all)	11	1	6
Oropharyngeal pain			
subjects affected / exposed	10 / 38 (26.32%)	1 / 11 (9.09%)	6 / 73 (8.22%)
occurrences (all)	12	1	7
Nasal congestion			
subjects affected / exposed	4 / 38 (10.53%)	1 / 11 (9.09%)	3 / 73 (4.11%)
occurrences (all)	5	1	5
Rhinorrhoea			
subjects affected / exposed	4 / 38 (10.53%)	1 / 11 (9.09%)	2 / 73 (2.74%)
occurrences (all)	4	1	2
Pleural effusion			
subjects affected / exposed	2 / 38 (5.26%)	1 / 11 (9.09%)	2 / 73 (2.74%)
occurrences (all)	2	2	2
Dysphonia			
subjects affected / exposed	2 / 38 (5.26%)	0 / 11 (0.00%)	1 / 73 (1.37%)
occurrences (all)	2	0	1
Rhinitis allergic			
subjects affected / exposed	3 / 38 (7.89%)	0 / 11 (0.00%)	0 / 73 (0.00%)
occurrences (all)	3	0	0
Hypoxia			

subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1	1 / 11 (9.09%) 1	1 / 73 (1.37%) 1
Pulmonary embolism subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1	1 / 11 (9.09%) 1	0 / 73 (0.00%) 0
Throat irritation subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1	1 / 11 (9.09%) 1	0 / 73 (0.00%) 0
Sinus disorder subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	1 / 11 (9.09%) 1	0 / 73 (0.00%) 0
Psychiatric disorders			
Insomnia subjects affected / exposed occurrences (all)	6 / 38 (15.79%) 6	2 / 11 (18.18%) 2	8 / 73 (10.96%) 8
Anxiety subjects affected / exposed occurrences (all)	3 / 38 (7.89%) 3	1 / 11 (9.09%) 1	11 / 73 (15.07%) 11
Depression subjects affected / exposed occurrences (all)	4 / 38 (10.53%) 4	1 / 11 (9.09%) 1	6 / 73 (8.22%) 7
Aggression subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	1 / 11 (9.09%) 1	0 / 73 (0.00%) 0
Product issues			
Device malfunction subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	1 / 11 (9.09%) 2	0 / 73 (0.00%) 0
Investigations			
Neutrophil count decreased subjects affected / exposed occurrences (all)	3 / 38 (7.89%) 4	0 / 11 (0.00%) 0	13 / 73 (17.81%) 22
Weight decreased subjects affected / exposed occurrences (all)	3 / 38 (7.89%) 3	0 / 11 (0.00%) 0	8 / 73 (10.96%) 11
White blood cell count decreased			

subjects affected / exposed	1 / 38 (2.63%)	1 / 11 (9.09%)	6 / 73 (8.22%)
occurrences (all)	2	6	14
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 38 (7.89%)	1 / 11 (9.09%)	1 / 73 (1.37%)
occurrences (all)	3	2	2
Alanine aminotransferase increased			
subjects affected / exposed	2 / 38 (5.26%)	0 / 11 (0.00%)	1 / 73 (1.37%)
occurrences (all)	3	0	2
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 38 (2.63%)	1 / 11 (9.09%)	2 / 73 (2.74%)
occurrences (all)	1	2	3
Blood pressure increased			
subjects affected / exposed	0 / 38 (0.00%)	1 / 11 (9.09%)	1 / 73 (1.37%)
occurrences (all)	0	1	1
Cardiac murmur			
subjects affected / exposed	2 / 38 (5.26%)	0 / 11 (0.00%)	0 / 73 (0.00%)
occurrences (all)	2	0	0
Granulocyte count decreased			
subjects affected / exposed	0 / 38 (0.00%)	1 / 11 (9.09%)	0 / 73 (0.00%)
occurrences (all)	0	2	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	8 / 38 (21.05%)	0 / 11 (0.00%)	1 / 73 (1.37%)
occurrences (all)	14	0	1
Limb injury			
subjects affected / exposed	2 / 38 (5.26%)	1 / 11 (9.09%)	0 / 73 (0.00%)
occurrences (all)	2	1	0
Skin abrasion			
subjects affected / exposed	3 / 38 (7.89%)	0 / 11 (0.00%)	0 / 73 (0.00%)
occurrences (all)	3	0	0
Fibula fracture			
subjects affected / exposed	0 / 38 (0.00%)	1 / 11 (9.09%)	0 / 73 (0.00%)
occurrences (all)	0	2	0
Procedural pain			

subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	1 / 11 (9.09%) 1	0 / 73 (0.00%) 0
Cardiac disorders			
Tachycardia			
subjects affected / exposed	5 / 38 (13.16%)	1 / 11 (9.09%)	1 / 73 (1.37%)
occurrences (all)	5	1	1
Palpitations			
subjects affected / exposed	3 / 38 (7.89%)	0 / 11 (0.00%)	0 / 73 (0.00%)
occurrences (all)	5	0	0
Nervous system disorders			
Neuropathy peripheral			
subjects affected / exposed	8 / 38 (21.05%)	4 / 11 (36.36%)	12 / 73 (16.44%)
occurrences (all)	8	4	15
Headache			
subjects affected / exposed	6 / 38 (15.79%)	1 / 11 (9.09%)	8 / 73 (10.96%)
occurrences (all)	9	1	11
Dizziness			
subjects affected / exposed	8 / 38 (21.05%)	0 / 11 (0.00%)	10 / 73 (13.70%)
occurrences (all)	14	0	16
Peripheral sensory neuropathy			
subjects affected / exposed	4 / 38 (10.53%)	2 / 11 (18.18%)	9 / 73 (12.33%)
occurrences (all)	4	2	9
Dysgeusia			
subjects affected / exposed	7 / 38 (18.42%)	0 / 11 (0.00%)	4 / 73 (5.48%)
occurrences (all)	9	0	4
Somnolence			
subjects affected / exposed	2 / 38 (5.26%)	1 / 11 (9.09%)	7 / 73 (9.59%)
occurrences (all)	3	1	9
Paraesthesia			
subjects affected / exposed	2 / 38 (5.26%)	0 / 11 (0.00%)	1 / 73 (1.37%)
occurrences (all)	2	0	1
Restless legs syndrome			
subjects affected / exposed	3 / 38 (7.89%)	0 / 11 (0.00%)	3 / 73 (4.11%)
occurrences (all)	3	0	3
Memory impairment			

subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2	0 / 11 (0.00%) 0	1 / 73 (1.37%) 1
Amnesia subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1	1 / 11 (9.09%) 1	1 / 73 (1.37%) 1
Hyperaesthesia subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2	0 / 11 (0.00%) 0	0 / 73 (0.00%) 0
Tremor subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2	0 / 11 (0.00%) 0	1 / 73 (1.37%) 1
Blood and lymphatic system disorders			
Neutropenia subjects affected / exposed occurrences (all)	24 / 38 (63.16%) 100	10 / 11 (90.91%) 58	52 / 73 (71.23%) 179
Anaemia subjects affected / exposed occurrences (all)	22 / 38 (57.89%) 37	7 / 11 (63.64%) 13	33 / 73 (45.21%) 61
Leukopenia subjects affected / exposed occurrences (all)	20 / 38 (52.63%) 47	8 / 11 (72.73%) 32	11 / 73 (15.07%) 27
Thrombocytopenia subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	2 / 11 (18.18%) 17	4 / 73 (5.48%) 7
Granulocytopenia subjects affected / exposed occurrences (all)	3 / 38 (7.89%) 4	1 / 11 (9.09%) 4	0 / 73 (0.00%) 0
Febrile neutropenia subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1	1 / 11 (9.09%) 1	1 / 73 (1.37%) 1
Ear and labyrinth disorders			
Ear pain subjects affected / exposed occurrences (all)	3 / 38 (7.89%) 4	0 / 11 (0.00%) 0	3 / 73 (4.11%) 3
Ear congestion			

subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	1 / 11 (9.09%) 1	0 / 73 (0.00%) 0
Eye disorders			
Dry eye			
subjects affected / exposed	4 / 38 (10.53%)	2 / 11 (18.18%)	1 / 73 (1.37%)
occurrences (all)	5	2	1
Lacrimation increased			
subjects affected / exposed	2 / 38 (5.26%)	2 / 11 (18.18%)	2 / 73 (2.74%)
occurrences (all)	2	2	2
Visual impairment			
subjects affected / exposed	3 / 38 (7.89%)	1 / 11 (9.09%)	1 / 73 (1.37%)
occurrences (all)	3	1	1
Cataract			
subjects affected / exposed	1 / 38 (2.63%)	1 / 11 (9.09%)	2 / 73 (2.74%)
occurrences (all)	1	1	2
Eye pruritus			
subjects affected / exposed	2 / 38 (5.26%)	0 / 11 (0.00%)	1 / 73 (1.37%)
occurrences (all)	2	0	1
Vision blurred			
subjects affected / exposed	2 / 38 (5.26%)	0 / 11 (0.00%)	1 / 73 (1.37%)
occurrences (all)	4	0	1
Vitreous floaters			
subjects affected / exposed	1 / 38 (2.63%)	1 / 11 (9.09%)	0 / 73 (0.00%)
occurrences (all)	1	1	0
Conjunctivitis allergic			
subjects affected / exposed	0 / 38 (0.00%)	1 / 11 (9.09%)	0 / 73 (0.00%)
occurrences (all)	0	1	0
Meibomian gland dysfunction			
subjects affected / exposed	0 / 38 (0.00%)	1 / 11 (9.09%)	0 / 73 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	27 / 38 (71.05%)	8 / 11 (72.73%)	46 / 73 (63.01%)
occurrences (all)	49	11	96
Nausea			

subjects affected / exposed	23 / 38 (60.53%)	5 / 11 (45.45%)	32 / 73 (43.84%)
occurrences (all)	33	6	54
Stomatitis			
subjects affected / exposed	15 / 38 (39.47%)	8 / 11 (72.73%)	46 / 73 (63.01%)
occurrences (all)	32	10	91
Constipation			
subjects affected / exposed	15 / 38 (39.47%)	3 / 11 (27.27%)	26 / 73 (35.62%)
occurrences (all)	22	4	33
Abdominal pain			
subjects affected / exposed	12 / 38 (31.58%)	3 / 11 (27.27%)	21 / 73 (28.77%)
occurrences (all)	19	3	39
Vomiting			
subjects affected / exposed	13 / 38 (34.21%)	4 / 11 (36.36%)	20 / 73 (27.40%)
occurrences (all)	42	4	31
Abdominal pain upper			
subjects affected / exposed	3 / 38 (7.89%)	1 / 11 (9.09%)	11 / 73 (15.07%)
occurrences (all)	5	1	12
Dyspepsia			
subjects affected / exposed	5 / 38 (13.16%)	1 / 11 (9.09%)	9 / 73 (12.33%)
occurrences (all)	5	1	12
Abdominal distension			
subjects affected / exposed	2 / 38 (5.26%)	2 / 11 (18.18%)	9 / 73 (12.33%)
occurrences (all)	2	2	10
Ascites			
subjects affected / exposed	3 / 38 (7.89%)	1 / 11 (9.09%)	8 / 73 (10.96%)
occurrences (all)	3	1	11
Haemorrhoids			
subjects affected / exposed	4 / 38 (10.53%)	0 / 11 (0.00%)	9 / 73 (12.33%)
occurrences (all)	4	0	10
Gastrooesophageal reflux disease			
subjects affected / exposed	4 / 38 (10.53%)	0 / 11 (0.00%)	6 / 73 (8.22%)
occurrences (all)	4	0	7
Oral pain			
subjects affected / exposed	5 / 38 (13.16%)	0 / 11 (0.00%)	6 / 73 (8.22%)
occurrences (all)	6	0	6
Dry mouth			

subjects affected / exposed	3 / 38 (7.89%)	2 / 11 (18.18%)	1 / 73 (1.37%)
occurrences (all)	3	2	1
Abdominal discomfort			
subjects affected / exposed	5 / 38 (13.16%)	2 / 11 (18.18%)	1 / 73 (1.37%)
occurrences (all)	6	2	1
Flatulence			
subjects affected / exposed	6 / 38 (15.79%)	1 / 11 (9.09%)	1 / 73 (1.37%)
occurrences (all)	9	3	1
Aphthous stomatitis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 11 (0.00%)	5 / 73 (6.85%)
occurrences (all)	0	0	9
Dysphagia			
subjects affected / exposed	1 / 38 (2.63%)	1 / 11 (9.09%)	4 / 73 (5.48%)
occurrences (all)	1	1	6
Toothache			
subjects affected / exposed	2 / 38 (5.26%)	0 / 11 (0.00%)	2 / 73 (2.74%)
occurrences (all)	2	0	2
Rectal haemorrhage			
subjects affected / exposed	2 / 38 (5.26%)	0 / 11 (0.00%)	2 / 73 (2.74%)
occurrences (all)	2	0	2
Abdominal pain lower			
subjects affected / exposed	2 / 38 (5.26%)	0 / 11 (0.00%)	0 / 73 (0.00%)
occurrences (all)	4	0	0
Tongue ulceration			
subjects affected / exposed	1 / 38 (2.63%)	1 / 11 (9.09%)	1 / 73 (1.37%)
occurrences (all)	1	1	2
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	26 / 38 (68.42%)	5 / 11 (45.45%)	28 / 73 (38.36%)
occurrences (all)	29	6	36
Rash			
subjects affected / exposed	8 / 38 (21.05%)	2 / 11 (18.18%)	5 / 73 (6.85%)
occurrences (all)	9	2	5
Dry skin			
subjects affected / exposed	4 / 38 (10.53%)	1 / 11 (9.09%)	5 / 73 (6.85%)
occurrences (all)	4	1	5

Pruritus			
subjects affected / exposed	4 / 38 (10.53%)	0 / 11 (0.00%)	5 / 73 (6.85%)
occurrences (all)	5	0	5
Erythema			
subjects affected / exposed	5 / 38 (13.16%)	1 / 11 (9.09%)	2 / 73 (2.74%)
occurrences (all)	6	1	2
Nail disorder			
subjects affected / exposed	4 / 38 (10.53%)	3 / 11 (27.27%)	1 / 73 (1.37%)
occurrences (all)	4	3	1
Onycholysis			
subjects affected / exposed	2 / 38 (5.26%)	0 / 11 (0.00%)	2 / 73 (2.74%)
occurrences (all)	2	0	2
Skin lesion			
subjects affected / exposed	6 / 38 (15.79%)	0 / 11 (0.00%)	1 / 73 (1.37%)
occurrences (all)	12	0	3
Skin exfoliation			
subjects affected / exposed	4 / 38 (10.53%)	1 / 11 (9.09%)	0 / 73 (0.00%)
occurrences (all)	4	1	0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 38 (2.63%)	1 / 11 (9.09%)	2 / 73 (2.74%)
occurrences (all)	1	1	2
Pruritus generalised			
subjects affected / exposed	2 / 38 (5.26%)	1 / 11 (9.09%)	1 / 73 (1.37%)
occurrences (all)	2	1	1
Rash macular			
subjects affected / exposed	2 / 38 (5.26%)	0 / 11 (0.00%)	1 / 73 (1.37%)
occurrences (all)	2	0	4
Rash pruritic			
subjects affected / exposed	3 / 38 (7.89%)	0 / 11 (0.00%)	1 / 73 (1.37%)
occurrences (all)	3	0	1
Nail discolouration			
subjects affected / exposed	0 / 38 (0.00%)	1 / 11 (9.09%)	2 / 73 (2.74%)
occurrences (all)	0	1	2
Rash erythematous			

subjects affected / exposed	2 / 38 (5.26%)	0 / 11 (0.00%)	1 / 73 (1.37%)
occurrences (all)	3	0	1
Dermatitis contact			
subjects affected / exposed	1 / 38 (2.63%)	1 / 11 (9.09%)	0 / 73 (0.00%)
occurrences (all)	1	1	0
Hyperhidrosis			
subjects affected / exposed	2 / 38 (5.26%)	0 / 11 (0.00%)	0 / 73 (0.00%)
occurrences (all)	3	0	0
Skin ulcer			
subjects affected / exposed	2 / 38 (5.26%)	0 / 11 (0.00%)	0 / 73 (0.00%)
occurrences (all)	10	0	0
Solar dermatitis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 11 (9.09%)	0 / 73 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 38 (2.63%)	2 / 11 (18.18%)	3 / 73 (4.11%)
occurrences (all)	1	2	3
Dysuria			
subjects affected / exposed	2 / 38 (5.26%)	1 / 11 (9.09%)	4 / 73 (5.48%)
occurrences (all)	2	1	12
Pollakiuria			
subjects affected / exposed	2 / 38 (5.26%)	1 / 11 (9.09%)	3 / 73 (4.11%)
occurrences (all)	2	1	3
Bladder spasm			
subjects affected / exposed	3 / 38 (7.89%)	0 / 11 (0.00%)	2 / 73 (2.74%)
occurrences (all)	3	0	2
Acute kidney injury			
subjects affected / exposed	2 / 38 (5.26%)	0 / 11 (0.00%)	0 / 73 (0.00%)
occurrences (all)	2	0	0
Proteinuria			
subjects affected / exposed	1 / 38 (2.63%)	1 / 11 (9.09%)	0 / 73 (0.00%)
occurrences (all)	1	1	0
Renal failure			
subjects affected / exposed	2 / 38 (5.26%)	0 / 11 (0.00%)	0 / 73 (0.00%)
occurrences (all)	2	0	0

Cystitis noninfective subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	1 / 11 (9.09%) 1	0 / 73 (0.00%) 0
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	1 / 11 (9.09%) 1	0 / 73 (0.00%) 0
Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed occurrences (all)	10 / 38 (26.32%) 15	2 / 11 (18.18%) 7	9 / 73 (12.33%) 11
Arthralgia subjects affected / exposed occurrences (all)	11 / 38 (28.95%) 18	3 / 11 (27.27%) 3	7 / 73 (9.59%) 9
Pain in extremity subjects affected / exposed occurrences (all)	7 / 38 (18.42%) 14	1 / 11 (9.09%) 1	8 / 73 (10.96%) 9
Muscle spasms subjects affected / exposed occurrences (all)	3 / 38 (7.89%) 7	0 / 11 (0.00%) 0	4 / 73 (5.48%) 4
Back pain subjects affected / exposed occurrences (all)	5 / 38 (13.16%) 10	1 / 11 (9.09%) 1	4 / 73 (5.48%) 4
Musculoskeletal pain subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2	1 / 11 (9.09%) 1	3 / 73 (4.11%) 5
Neck pain subjects affected / exposed occurrences (all)	3 / 38 (7.89%) 4	0 / 11 (0.00%) 0	4 / 73 (5.48%) 5
Muscular weakness subjects affected / exposed occurrences (all)	6 / 38 (15.79%) 9	0 / 11 (0.00%) 0	0 / 73 (0.00%) 0
Flank pain subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2	0 / 11 (0.00%) 0	1 / 73 (1.37%) 1
Bone pain			

subjects affected / exposed	2 / 38 (5.26%)	0 / 11 (0.00%)	2 / 73 (2.74%)
occurrences (all)	2	0	4
Musculoskeletal chest pain			
subjects affected / exposed	2 / 38 (5.26%)	0 / 11 (0.00%)	1 / 73 (1.37%)
occurrences (all)	2	0	1
Pain in jaw			
subjects affected / exposed	3 / 38 (7.89%)	0 / 11 (0.00%)	0 / 73 (0.00%)
occurrences (all)	8	0	0
Musculoskeletal discomfort			
subjects affected / exposed	2 / 38 (5.26%)	0 / 11 (0.00%)	0 / 73 (0.00%)
occurrences (all)	2	0	0
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	11 / 38 (28.95%)	4 / 11 (36.36%)	11 / 73 (15.07%)
occurrences (all)	29	8	20
Upper respiratory tract infection			
subjects affected / exposed	11 / 38 (28.95%)	4 / 11 (36.36%)	3 / 73 (4.11%)
occurrences (all)	24	4	4
Sinusitis			
subjects affected / exposed	3 / 38 (7.89%)	3 / 11 (27.27%)	1 / 73 (1.37%)
occurrences (all)	10	3	1
Oral candidiasis			
subjects affected / exposed	4 / 38 (10.53%)	0 / 11 (0.00%)	2 / 73 (2.74%)
occurrences (all)	4	0	2
Oral herpes			
subjects affected / exposed	2 / 38 (5.26%)	0 / 11 (0.00%)	2 / 73 (2.74%)
occurrences (all)	4	0	2
Bronchitis			
subjects affected / exposed	2 / 38 (5.26%)	0 / 11 (0.00%)	3 / 73 (4.11%)
occurrences (all)	2	0	3
Folliculitis			
subjects affected / exposed	5 / 38 (13.16%)	0 / 11 (0.00%)	0 / 73 (0.00%)
occurrences (all)	5	0	0
Candida infection			
subjects affected / exposed	0 / 38 (0.00%)	0 / 11 (0.00%)	4 / 73 (5.48%)
occurrences (all)	0	0	6

Cellulitis			
subjects affected / exposed	2 / 38 (5.26%)	0 / 11 (0.00%)	1 / 73 (1.37%)
occurrences (all)	5	0	1
Influenza			
subjects affected / exposed	0 / 38 (0.00%)	1 / 11 (9.09%)	2 / 73 (2.74%)
occurrences (all)	0	1	2
Localised infection			
subjects affected / exposed	3 / 38 (7.89%)	1 / 11 (9.09%)	0 / 73 (0.00%)
occurrences (all)	3	1	0
Pneumonia			
subjects affected / exposed	1 / 38 (2.63%)	1 / 11 (9.09%)	1 / 73 (1.37%)
occurrences (all)	1	1	1
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 38 (2.63%)	1 / 11 (9.09%)	0 / 73 (0.00%)
occurrences (all)	1	2	0
Catheter site cellulitis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 11 (9.09%)	0 / 73 (0.00%)
occurrences (all)	0	1	0
Skin candida			
subjects affected / exposed	0 / 38 (0.00%)	1 / 11 (9.09%)	0 / 73 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	12 / 38 (31.58%)	2 / 11 (18.18%)	15 / 73 (20.55%)
occurrences (all)	17	2	18
Hypokalaemia			
subjects affected / exposed	6 / 38 (15.79%)	4 / 11 (36.36%)	13 / 73 (17.81%)
occurrences (all)	8	5	27
Hypomagnesaemia			
subjects affected / exposed	8 / 38 (21.05%)	3 / 11 (27.27%)	8 / 73 (10.96%)
occurrences (all)	16	3	9
Dehydration			
subjects affected / exposed	7 / 38 (18.42%)	0 / 11 (0.00%)	8 / 73 (10.96%)
occurrences (all)	8	0	9
Hyperglycaemia			

subjects affected / exposed	2 / 38 (5.26%)	1 / 11 (9.09%)	2 / 73 (2.74%)
occurrences (all)	3	3	2
Hyponatraemia			
subjects affected / exposed	1 / 38 (2.63%)	1 / 11 (9.09%)	4 / 73 (5.48%)
occurrences (all)	1	1	4
Hypophosphataemia			
subjects affected / exposed	2 / 38 (5.26%)	1 / 11 (9.09%)	3 / 73 (4.11%)
occurrences (all)	3	1	3
Hypocalcaemia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 11 (9.09%)	0 / 73 (0.00%)
occurrences (all)	0	1	0
Hypoalbuminaemia			
subjects affected / exposed	1 / 38 (2.63%)	1 / 11 (9.09%)	0 / 73 (0.00%)
occurrences (all)	1	1	0
Hypercalcaemia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 11 (9.09%)	0 / 73 (0.00%)
occurrences (all)	0	4	0
Hyperkalaemia			
subjects affected / exposed	4 / 38 (10.53%)	0 / 11 (0.00%)	1 / 73 (1.37%)
occurrences (all)	4	0	2

Non-serious adverse events	Paclitaxel 80 mg/m ² (Phase 2)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	64 / 69 (92.75%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences (all)	2		
Hot flush			
subjects affected / exposed	2 / 69 (2.90%)		
occurrences (all)	3		
Hypotension			

subjects affected / exposed	2 / 69 (2.90%)		
occurrences (all)	2		
Deep vein thrombosis			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences (all)	1		
Lymphoedema			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Orthostatic hypotension			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Blood pressure fluctuation			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Superior vena cava stenosis			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	31 / 69 (44.93%)		
occurrences (all)	37		
Oedema peripheral			
subjects affected / exposed	18 / 69 (26.09%)		
occurrences (all)	25		
Pyrexia			
subjects affected / exposed	7 / 69 (10.14%)		
occurrences (all)	10		
Asthenia			
subjects affected / exposed	8 / 69 (11.59%)		
occurrences (all)	11		
Chills			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Non-cardiac chest pain			

subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Catheter site pain			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences (all)	1		
Peripheral swelling			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences (all)	1		
Chest discomfort			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Early satiety			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Localised oedema			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	2 / 69 (2.90%)		
occurrences (all)	2		
Genital discomfort			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Vulvovaginal pain			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Cystocele			

subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Postmenopausal haemorrhage			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 69 (5.80%)		
occurrences (all)	4		
Dyspnoea			
subjects affected / exposed	11 / 69 (15.94%)		
occurrences (all)	19		
Epistaxis			
subjects affected / exposed	7 / 69 (10.14%)		
occurrences (all)	11		
Oropharyngeal pain			
subjects affected / exposed	2 / 69 (2.90%)		
occurrences (all)	2		
Nasal congestion			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Rhinorrhoea			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Pleural effusion			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences (all)	1		
Dysphonia			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences (all)	1		
Rhinitis allergic			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences (all)	2		
Hypoxia			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pulmonary embolism</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Throat irritation</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Sinus disorder</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 69 (0.00%)</p> <p>0</p> <p>1 / 69 (1.45%)</p> <p>1</p> <p>0 / 69 (0.00%)</p> <p>0</p> <p>0 / 69 (0.00%)</p> <p>0</p>		
<p>Psychiatric disorders</p> <p>Insomnia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Anxiety</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Depression</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Aggression</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>7 / 69 (10.14%)</p> <p>8</p> <p>7 / 69 (10.14%)</p> <p>9</p> <p>4 / 69 (5.80%)</p> <p>4</p> <p>0 / 69 (0.00%)</p> <p>0</p>		
<p>Product issues</p> <p>Device malfunction</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 69 (0.00%)</p> <p>0</p>		
<p>Investigations</p> <p>Neutrophil count decreased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Weight decreased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>White blood cell count decreased</p>	<p>4 / 69 (5.80%)</p> <p>5</p> <p>2 / 69 (2.90%)</p> <p>2</p>		

subjects affected / exposed	1 / 69 (1.45%)		
occurrences (all)	1		
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 69 (4.35%)		
occurrences (all)	4		
Alanine aminotransferase increased			
subjects affected / exposed	4 / 69 (5.80%)		
occurrences (all)	4		
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 69 (2.90%)		
occurrences (all)	3		
Blood pressure increased			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Cardiac murmur			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Granulocyte count decreased			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	3 / 69 (4.35%)		
occurrences (all)	3		
Limb injury			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Skin abrasion			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Fibula fracture			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Procedural pain			

subjects affected / exposed occurrences (all)	0 / 69 (0.00%) 0		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	2 / 69 (2.90%)		
occurrences (all)	2		
Palpitations			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences (all)	1		
Nervous system disorders			
Neuropathy peripheral			
subjects affected / exposed	13 / 69 (18.84%)		
occurrences (all)	16		
Headache			
subjects affected / exposed	13 / 69 (18.84%)		
occurrences (all)	22		
Dizziness			
subjects affected / exposed	6 / 69 (8.70%)		
occurrences (all)	9		
Peripheral sensory neuropathy			
subjects affected / exposed	8 / 69 (11.59%)		
occurrences (all)	9		
Dysgeusia			
subjects affected / exposed	5 / 69 (7.25%)		
occurrences (all)	6		
Somnolence			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Paraesthesia			
subjects affected / exposed	5 / 69 (7.25%)		
occurrences (all)	8		
Restless legs syndrome			
subjects affected / exposed	2 / 69 (2.90%)		
occurrences (all)	2		
Memory impairment			

subjects affected / exposed	2 / 69 (2.90%)		
occurrences (all)	2		
Amnesia			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences (all)	1		
Hyperaesthesia			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Tremor			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	10 / 69 (14.49%)		
occurrences (all)	17		
Anaemia			
subjects affected / exposed	20 / 69 (28.99%)		
occurrences (all)	36		
Leukopenia			
subjects affected / exposed	3 / 69 (4.35%)		
occurrences (all)	6		
Thrombocytopenia			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences (all)	2		
Granulocytopenia			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences (all)	1		
Febrile neutropenia			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences (all)	1		
Ear congestion			

subjects affected / exposed	1 / 69 (1.45%)		
occurrences (all)	1		
Eye disorders			
Dry eye			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences (all)	1		
Lacrimation increased			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences (all)	1		
Visual impairment			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Cataract			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Eye pruritus			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences (all)	1		
Vision blurred			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences (all)	1		
Vitreous floaters			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Conjunctivitis allergic			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Meibomian gland dysfunction			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	15 / 69 (21.74%)		
occurrences (all)	19		
Nausea			

subjects affected / exposed	32 / 69 (46.38%)		
occurrences (all)	46		
Stomatitis			
subjects affected / exposed	6 / 69 (8.70%)		
occurrences (all)	8		
Constipation			
subjects affected / exposed	17 / 69 (24.64%)		
occurrences (all)	23		
Abdominal pain			
subjects affected / exposed	20 / 69 (28.99%)		
occurrences (all)	26		
Vomiting			
subjects affected / exposed	18 / 69 (26.09%)		
occurrences (all)	25		
Abdominal pain upper			
subjects affected / exposed	4 / 69 (5.80%)		
occurrences (all)	6		
Dyspepsia			
subjects affected / exposed	3 / 69 (4.35%)		
occurrences (all)	3		
Abdominal distension			
subjects affected / exposed	4 / 69 (5.80%)		
occurrences (all)	4		
Ascites			
subjects affected / exposed	5 / 69 (7.25%)		
occurrences (all)	7		
Haemorrhoids			
subjects affected / exposed	2 / 69 (2.90%)		
occurrences (all)	4		
Gastrooesophageal reflux disease			
subjects affected / exposed	4 / 69 (5.80%)		
occurrences (all)	5		
Oral pain			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Dry mouth			

subjects affected / exposed	3 / 69 (4.35%)		
occurrences (all)	3		
Abdominal discomfort			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Flatulence			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Aphthous stomatitis			
subjects affected / exposed	2 / 69 (2.90%)		
occurrences (all)	2		
Dysphagia			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences (all)	2		
Toothache			
subjects affected / exposed	2 / 69 (2.90%)		
occurrences (all)	4		
Rectal haemorrhage			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Abdominal pain lower			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences (all)	1		
Tongue ulceration			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	22 / 69 (31.88%)		
occurrences (all)	24		
Rash			
subjects affected / exposed	2 / 69 (2.90%)		
occurrences (all)	2		
Dry skin			
subjects affected / exposed	2 / 69 (2.90%)		
occurrences (all)	2		

Pruritus			
subjects affected / exposed	2 / 69 (2.90%)		
occurrences (all)	4		
Erythema			
subjects affected / exposed	2 / 69 (2.90%)		
occurrences (all)	4		
Nail disorder			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Onycholysis			
subjects affected / exposed	3 / 69 (4.35%)		
occurrences (all)	3		
Skin lesion			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Skin exfoliation			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Pruritus generalised			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Rash macular			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences (all)	1		
Rash pruritic			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Nail discolouration			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Rash erythematous			

subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Dermatitis contact			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Hyperhidrosis			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Skin ulcer			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Solar dermatitis			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	5 / 69 (7.25%)		
occurrences (all)	5		
Dysuria			
subjects affected / exposed	3 / 69 (4.35%)		
occurrences (all)	9		
Pollakiuria			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences (all)	1		
Bladder spasm			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Acute kidney injury			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Proteinuria			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Renal failure			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		

Cystitis noninfective subjects affected / exposed occurrences (all)	0 / 69 (0.00%) 0		
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	0 / 69 (0.00%) 0		
Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed occurrences (all)	9 / 69 (13.04%) 13		
Arthralgia subjects affected / exposed occurrences (all)	6 / 69 (8.70%) 9		
Pain in extremity subjects affected / exposed occurrences (all)	5 / 69 (7.25%) 6		
Muscle spasms subjects affected / exposed occurrences (all)	7 / 69 (10.14%) 9		
Back pain subjects affected / exposed occurrences (all)	3 / 69 (4.35%) 3		
Musculoskeletal pain subjects affected / exposed occurrences (all)	2 / 69 (2.90%) 2		
Neck pain subjects affected / exposed occurrences (all)	1 / 69 (1.45%) 1		
Muscular weakness subjects affected / exposed occurrences (all)	1 / 69 (1.45%) 3		
Flank pain subjects affected / exposed occurrences (all)	3 / 69 (4.35%) 3		
Bone pain			

subjects affected / exposed	1 / 69 (1.45%)		
occurrences (all)	1		
Musculoskeletal chest pain			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Pain in jaw			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Musculoskeletal discomfort			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	4 / 69 (5.80%)		
occurrences (all)	7		
Upper respiratory tract infection			
subjects affected / exposed	4 / 69 (5.80%)		
occurrences (all)	5		
Sinusitis			
subjects affected / exposed	2 / 69 (2.90%)		
occurrences (all)	2		
Oral candidiasis			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences (all)	1		
Oral herpes			
subjects affected / exposed	2 / 69 (2.90%)		
occurrences (all)	2		
Bronchitis			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Folliculitis			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Candida infection			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		

Cellulitis			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences (all)	1		
Localised infection			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Pneumonia			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Catheter site cellulitis			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Skin candida			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	8 / 69 (11.59%)		
occurrences (all)	11		
Hypokalaemia			
subjects affected / exposed	4 / 69 (5.80%)		
occurrences (all)	5		
Hypomagnesaemia			
subjects affected / exposed	7 / 69 (10.14%)		
occurrences (all)	8		
Dehydration			
subjects affected / exposed	3 / 69 (4.35%)		
occurrences (all)	4		
Hyperglycaemia			

subjects affected / exposed	2 / 69 (2.90%)		
occurrences (all)	3		
Hyponatraemia			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences (all)	1		
Hypophosphataemia			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Hypocalcaemia			
subjects affected / exposed	2 / 69 (2.90%)		
occurrences (all)	3		
Hypoalbuminaemia			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Hypercalcaemia			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Hyperkalaemia			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 December 2009	<ul style="list-style-type: none">• Changed the study drug from the powder-in-capsule (PIC) to the enteric coated tablet (ECT) formulation• Modified the alisertib dosing schedule from consecutive daily dosing to intermittent dosing• Increase the sample size in phase 1 from 20 to 30, and to decrease the number of study centers in phase 2 from 50 to 30• Increased the duration of the phase 1 portion from 18 to 22 months, including an increase in the duration of the enrollment period from 6 to 10 months
15 November 2010	<ul style="list-style-type: none">• Specified that subjects in the phase 1 portion could be followed until 110 progression-free survival (PFS) events were achieved in phase 2• Added antineoplastic therapy as a reason to discontinue treatment with alisertib, paclitaxel, or combination therapy (alisertib + paclitaxel)• Allowed continued protocol treatment up to 24 months
30 November 2010	<ul style="list-style-type: none">• Allowed subjects that could have been maintained on study treatment after disease progression (PD) in selected circumstances and to define the criteria for withdrawing subjects from study treatment
27 April 2012	<ul style="list-style-type: none">• Provided the RP2D for the combination arm in phase 2 as determined from the phase 1 portion of the study

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported