# 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 |

**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/m^2 or single-agent paclitaxel 80 mg/m^2.

### 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/m^2, 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) |

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/m^2, 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:<br>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:<br>Paclitaxel Intravenous Infusion | |
| **Arm title** | Alisertib 40 mg BID+ Paclitaxel 60 mg/m^2 (Phase 2) |
| Arm description:<br>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:<br>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:<br>Paclitaxel intravenous Infusion | |
| **Arm title** | Paclitaxel 80 mg/m^2 (Phase 2) |
| Arm description:<br>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:<br>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/m^2 (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) |
| 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). | |

| 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<br>Units: Subjects | | | |
| Age Continuous<br>Units: years | | | |
| arithmetic mean | 55.8 | 58.6 | 61.0 |
| standard deviation | ± 10.29 | ± 10.06 | ± 11.60 |
| Gender, Male/Female<br>Units: Subjects | | | |
| Female | 38 | 11 | 73 |
| Male | 0 | 0 | 0 |
| Race/Ethnicity, Customized<br>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<br>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<br>Units: Subjects | | | |
| United States | 38 | 11 | 48 |
| Poland | 0 | 0 | 10 |
| France | 0 | 0 | 15 |
| Height<br>Units: cm | | | |
| arithmetic mean | 164.2 | 164.5 | 162.4 |
| standard deviation | ± 6.41 | ± 6.38 | ± 7.02 |
| Weight<br>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<br>Units: Subjects | | | |
| Age Continuous<br>Units: years | | | |
| arithmetic mean | 60.8 | | |
| standard deviation | ± 8.41 | - | |
| Gender, Male/Female<br>Units: Subjects | | | |
| Female | 69 | 191 | |
| Male | 0 | 0 | |
| Race/Ethnicity, Customized<br>Units: Subjects | | | |
| Hispanic or Latino | 4 | 9 | |
| Not Hispanic or Latino | 62 | 170 | |
| Not Reported | 3 | 11 | |
| Missing | 0 | 1 | |
| Race/Ethnicity, Customized<br>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<br>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 | |
| 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/m^2, 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/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 (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/m^2, 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] |
|---|---|

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/mm^3; 4.Grade 3 thrombocytopenia with bleeding; 5.Any other ≥Grade3 nonhematologic toxicity, with exceptions: ≥Grade3 nausea/emesis, ≥Grade3 diarrhoea, Grade3 fatigue, Grade3 nonhematological toxicity that is controlled to ≤Grade 2 with appropriate treatment; 6.Other alisertib-related nonhematologic toxicities ≥Grade2 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 |
|---|---|

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] |
|---|---|

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] |
|---|---|

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] |
|---|---|

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 |
|---|---|

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] |
|---|---|

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 |
|---|---|

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] |
|---|---|

End point description:

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

| End point type | Primary |
|---|---|

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] |
|---|---|

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 |
|---|---|

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] |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 + | | |
|---|---|---|---|---|

| | 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 |
|---|---|

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 |
|---|---|

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 |

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 |

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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: 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: t½: Terminal Half-Life for Paclitaxel in Phase 1

| End point title | t½: Terminal Half-Life for Paclitaxel in Phase 1 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 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 |
|---|---|

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) | 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 |
|---|---|

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] |
|---|---|

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 |
|---|---|

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] |
|---|---|

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 |
|---|---|

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] |
|---|---|

End point description:

OS was defined as the time form 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 |
|---|---|

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] |
|---|---|

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 |
|---|---|

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] |
|---|---|

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 |
|---|---|

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] |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 20.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Alisertib (Phase 1 - Ovarian cancer) |

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/m^2, intravenous infusion, weekly (Days 1, 8, 15) in 28-day cycles in Phase 1.

| | |
|---|---|
| Reporting group title | Alisertib (Phase 1 - Breast cancer) |

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/m^2, 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) |

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).

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

| | | | |
|---|---|---|---|
| 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 | | | |

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

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|---|---|---|---|
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 11 (9.09%) | 0 / 73 (0.00%) |
| occurrences (all) | 0 | 1 | 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 | | | |

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

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|---|---|---|---|
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 11 (9.09%) | 0 / 73 (0.00%) |
| occurrences (all) | 0 | 1 | 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 | | | |

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

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

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

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