



Clinical trial results:

A Phase 3, Randomized, Two-Arm, Open-Label, Multicenter, International Trial of Alisertib (MLN8237) or Investigator's Choice (Selected Single Agent) in Patients With Relapsed or Refractory Peripheral T-Cell Lymphoma

Summary

| | |
|--------------------------|----------------------------------------|
| EudraCT number | 2011-003545-18 |
| Trial protocol | SE CZ PT DE HU AT GB ES DK NL BG IT BE |
| Global end of trial date | 18 December 2017 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 27 July 2018 |
| First version publication date | 27 July 2018 |

Trial information

Trial identification

| | |
|-----------------------|--------|
| Sponsor protocol code | C14012 |
|-----------------------|--------|

Additional study identifiers

| | |
|------------------------------------|-----------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01482962 |
| WHO universal trial number (UTN) | U1111-1181-8218 |

Notes:

Sponsors

| | |
|------------------------------|----------------------------------------------------------------------|
| Sponsor organisation name | Takeda Oncology |
| Sponsor organisation address | 40 Landsdowne Street, Cambridge, United States, MA 02139 |
| Public contact | Medical Director, Takeda, +1 8778253327, trialdisclosures@takeda.com |
| Scientific contact | Medical Director, Takeda, +1 8778253327, 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 | 18 December 2017 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 18 December 2017 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

This is a phase 3, randomized, 2-arm, open-label, international trial evaluating alisertib compared with single-agent treatment, as selected by the investigator from the offered options of pralatrexate or gemcitabine or romidepsin, in participants with relapsed or refractory peripheral T-cell lymphoma (PTCL). Note: romidepsin was not used as a single-agent comparator outside the United States of America (USA) as supply was not available.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

| | |
|-----------------------------------------------------------|--------------|
| Actual start date of recruitment | 11 June 2012 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Australia: 9 |
| Country: Number of subjects enrolled | Austria: 4 |
| Country: Number of subjects enrolled | Belgium: 8 |
| Country: Number of subjects enrolled | Brazil: 22 |
| Country: Number of subjects enrolled | Bulgaria: 1 |
| Country: Number of subjects enrolled | Canada: 3 |
| Country: Number of subjects enrolled | Czech Republic: 7 |
| Country: Number of subjects enrolled | Denmark: 5 |
| Country: Number of subjects enrolled | France: 8 |
| Country: Number of subjects enrolled | Germany: 7 |
| Country: Number of subjects enrolled | Hungary: 16 |
| Country: Number of subjects enrolled | Israel: 3 |
| Country: Number of subjects enrolled | Italy: 12 |
| Country: Number of subjects enrolled | Mexico: 4 |
| Country: Number of subjects enrolled | Netherlands: 1 |
| Country: Number of subjects enrolled | New Zealand: 5 |
| Country: Number of subjects enrolled | Peru: 4 |
| Country: Number of subjects enrolled | Poland: 10 |
| Country: Number of subjects enrolled | Portugal: 2 |

| | |
|--------------------------------------|-----------------------|
| Country: Number of subjects enrolled | Puerto Rico: 1 |
| Country: Number of subjects enrolled | Romania: 3 |
| Country: Number of subjects enrolled | Russian Federation: 8 |
| Country: Number of subjects enrolled | Spain: 25 |
| Country: Number of subjects enrolled | Sweden: 3 |
| Country: Number of subjects enrolled | Turkey: 21 |
| Country: Number of subjects enrolled | United States: 68 |
| Country: Number of subjects enrolled | United Kingdom: 11 |
| Worldwide total number of subjects | 271 |
| EEA total number of subjects | 123 |

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) | 147 |
| From 65 to 84 years | 122 |
| 85 years and over | 2 |

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 105 investigative sites in the United States including Puerto Rico, Canada, European Union, Russian Federation, Turkey, Israel, Australia, New Zealand and Latin America from 11 June 2012 to the end of study on 18 December 2017. This study is completed.

Pre-assignment

Screening details:

Participants with a diagnosis of Relapsed or Refractory Peripheral T-Cell Lymphoma were randomized 1:1 to either alisertib or comparator (investigator's choice of pralatrexate, romidepsin [USA only], or gemcitabine).

Period 1

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

Arms

| | |
|------------------------------|-----------|
| Are arms mutually exclusive? | Yes |
| Arm title | Alisertib |

Arm description:

Alisertib 50 mg, enteric-coated tablet formulation, orally, twice daily for 7 consecutive days (Cycle Days 1-7) in a 21-day cycle (Up to 148 Weeks).

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

| | |
|------------------|---------------------------------------------|
| Arm title | Pralatrexate, or Romidepsin, or Gemcitabine |
|------------------|---------------------------------------------|

Arm description:

Pralatrexate 30 mg/m², intravenous (IV) push over 3 to 5 minutes, once weekly, for 6 weeks in 7-week cycles with concurrent vitamin B12 and folic acid supplementation. Cycles were repeated every 7-weeks provided the participant continued to benefit from and tolerate the therapy (Up to 115 Weeks), or Gemcitabine 1,000 mg/m² over 30 minutes, intravenously, on Days 1, 8, and 15 of a 28-day cycle until the absence of disease progression or unacceptable toxicity (Up to 32 Weeks), or Romidepsin 14 mg/m², intravenously over a 4-hour period, on Days 1, 8, and 15 of a 28-cycle. Cycles were repeated every 28 days provided the patient continued to benefit from and tolerate the therapy (Up to 30 Weeks).

| | |
|----------------------------------------|------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Pralatrexate |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Pralatrexate Intravenous

| | |
|----------------------------------------|-------------|
| Investigational medicinal product name | Gemcitabine |
| Investigational medicinal product code | |
| Other name | |

| | |
|----------------------------------------|------------------------|
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| Gemcitabine Intravenous | |
| Investigational medicinal product name | Romidepsin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| Romidepsin Intravenous | |

| Number of subjects in period 1 | Alisertib | Pralatrexate, or Romidepsin, or Gemcitabine |
|----------------------------------------|-----------|---------------------------------------------------|
| | | |
| Started | 138 | 133 |
| Safety Population: Received Study Drug | 137 | 127 |
| Completed | 0 | 0 |
| Not completed | 138 | 133 |
| Unsatisfactory Therapeutic Response | 37 | 23 |
| Withdrawal by Participant | 8 | 13 |
| Adverse event, non-fatal | 18 | 22 |
| Progressive Disease | 65 | 53 |
| Other Reason | 1 | 5 |
| Hematopoietic Stem Cell Transplant | 3 | 9 |
| Study Terminated by Sponsor | 5 | 2 |
| Did not Receive Study Drug | 1 | 6 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | Alisertib |
|-----------------------|-----------|

Reporting group description:

Alisertib 50 mg, enteric-coated tablet formulation, orally, twice daily for 7 consecutive days (Cycle Days 1-7) in a 21-day cycle (Up to 148 Weeks).

| | |
|-----------------------|---------------------------------------------|
| Reporting group title | Pralatrexate, or Romidepsin, or Gemcitabine |
|-----------------------|---------------------------------------------|

Reporting group description:

Pralatrexate 30 mg/m², intravenous (IV) push over 3 to 5 minutes, once weekly, for 6 weeks in 7-week cycles with concurrent vitamin B12 and folic acid supplementation. Cycles were repeated every 7-weeks provided the participant continued to benefit from and tolerate the therapy (Up to 115 Weeks), or Gemcitabine 1,000 mg/m² over 30 minutes, intravenously, on Days 1, 8, and 15 of a 28-day cycle until the absence of disease progression or unacceptable toxicity (Up to 32 Weeks), or Romidepsin 14 mg/m², intravenously over a 4-hour period, on Days 1, 8, and 15 of a 28-cycle. Cycles were repeated every 28 days provided the patient continued to benefit from and tolerate the therapy (Up to 30 Weeks).

| Reporting group values | Alisertib | Pralatrexate, or Romidepsin, or Gemcitabine | Total |
|------------------------------------|-----------|---------------------------------------------------|-------|
| Number of subjects | 138 | 133 | 271 |
| Age categorical Units: Subjects | | | |

| | | | |
|-------------------------------------------------------------------------|-----------------|-----------------|-----|
| Age Continuous Units: years arithmetic mean standard deviation | 61.1 ± 12.69 | 61.4 ± 13.16 | - |
| Gender, Male/Female Units: Subjects | | | |
| Female | 46 | 47 | 93 |
| Male | 92 | 86 | 178 |
| Ethnicity (NIH/OMB) Units: Subjects | | | |
| Hispanic or Latino | 25 | 21 | 46 |
| Not Hispanic or Latino | 105 | 107 | 212 |
| Unknown or Not Reported | 8 | 5 | 13 |
| Race/Ethnicity, Customized Units: Subjects | | | |
| White | 115 | 114 | 229 |
| Black or African American | 8 | 8 | 16 |
| Asian | 3 | 2 | 5 |
| Other | 7 | 7 | 14 |
| Not Reported | 5 | 2 | 7 |
| Region of Enrollment Units: Subjects | | | |
| Australia | 5 | 4 | 9 |
| Austria | 2 | 2 | 4 |
| Belgium | 5 | 3 | 8 |
| Brazil | 12 | 10 | 22 |
| Bulgaria | 0 | 1 | 1 |

| | | | |
|-------------------------|----------|----------|----|
| Canada | 3 | 0 | 3 |
| Czech Republic | 5 | 2 | 7 |
| Denmark | 3 | 2 | 5 |
| France | 5 | 3 | 8 |
| Germany | 6 | 1 | 7 |
| Hungary | 9 | 7 | 16 |
| Israel | 0 | 3 | 3 |
| Italy | 6 | 6 | 12 |
| Mexico | 3 | 1 | 4 |
| Netherlands | 0 | 1 | 1 |
| New Zealand | 3 | 2 | 5 |
| Peru | 1 | 3 | 4 |
| Poland | 7 | 3 | 10 |
| Portugal | 1 | 1 | 2 |
| Puerto Rico | 0 | 1 | 1 |
| Romania | 2 | 1 | 3 |
| Russia | 4 | 4 | 8 |
| Spain | 14 | 11 | 25 |
| Sweden | 0 | 3 | 3 |
| Turkey | 10 | 11 | 21 |
| United Kingdom | 3 | 8 | 11 |
| United States | 29 | 39 | 68 |
| Height | | | |
| Units: cm | | | |
| arithmetic mean | 170.3 | 168.2 | |
| standard deviation | ± 9.80 | ± 8.99 | - |
| Weight | | | |
| Units: kg | | | |
| arithmetic mean | 76.85 | 74.63 | |
| standard deviation | ± 17.242 | ± 19.601 | - |
| Body Surface Area (BSA) | | | |
| Units: m ² | | | |
| arithmetic mean | 1.897 | 1.855 | |
| standard deviation | ± 0.2465 | ± 0.2562 | - |

End points

End points reporting groups

| | |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------|
| Reporting group title | Alisertib |
| Reporting group description: Alisertib 50 mg, enteric-coated tablet formulation, orally, twice daily for 7 consecutive days (Cycle Days 1-7) in a 21-day cycle (Up to 148 Weeks). | |
| Reporting group title | Pralatrexate, or Romidepsin, or Gemcitabine |
| Reporting group description: Pralatrexate 30 mg/m ² , intravenous (IV) push over 3 to 5 minutes, once weekly, for 6 weeks in 7-week cycles with concurrent vitamin B12 and folic acid supplementation. Cycles were repeated every 7-weeks provided the participant continued to benefit from and tolerate the therapy (Up to 115 Weeks), or Gemcitabine 1,000 mg/m ² over 30 minutes, intravenously, on Days 1, 8, and 15 of a 28-day cycle until the absence of disease progression or unacceptable toxicity (Up to 32 Weeks), or Romidepsin 14 mg/m ² , intravenously over a 4-hour period, on Days 1, 8, and 15 of a 28-cycle. Cycles were repeated every 28 days provided the patient continued to benefit from and tolerate the therapy (Up to 30 Weeks). | |

Primary: Overall Response Rate (ORR) based on Independent Review Committee (IRC) Assessment

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|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|
| End point title | Overall Response Rate (ORR) based on Independent Review Committee (IRC) Assessment |
| End point description: ORR was defined as the percentage of participants who achieve Complete Response (CR) or Partial Response (PR) as assessed by the IRC using International Working Group (IWG) criteria. CR=Disappearance of all evidence of disease and PR=Regression of measurable disease and no new sites. Response-evaluable population, participants with peripheral T-cell lymphoma confirmed by an independent hematopathology central review, with measurable disease at Baseline, who received at least 1 dose of alisertib or comparator and had postbaseline response assessment of CR, PR, stable disease (SD) or progressive disease (PD) by the IRC. | |
| End point type | Primary |
| End point timeframe: Every 8 weeks from date of first dose treatment; every 12 weeks after 40 week assessment; at end of treatment visit until progressive disease. Duration is approximately 3 years | |

| End point values | Alisertib | Pralatrexate, or Romidepsin, or Gemcitabine | | |
|-----------------------------------|-----------------|---------------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 102 | 92 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 33 (24 to 43) | 45 (34 to 55) | | |

Statistical analyses

| | |
|----------------------------|---------------------------------------------------------|
| Statistical analysis title | Statistical Analysis 1 |
| Comparison groups | Alisertib v Pralatrexate, or Romidepsin, or Gemcitabine |

| | |
|-----------------------------------------|-------------------------|
| Number of subjects included in analysis | 194 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.038 ^[1] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.33 |
| upper limit | 1.08 |

Notes:

[1] - P-value was stratified using disease type, International Prognostic Index (IPI) Score and region as stratification factors.

Primary: Progression-Free Survival (PFS) based on IRC Assessment

| | |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------|
| End point title | Progression-Free Survival (PFS) based on IRC Assessment |
| End point description: | |
| PFS was defined as the time from the date of randomization to the date of first documentation of progressive disease (PD) or death due to any cause, whichever occurred first. Intent-to-treat (ITT) population was defined as all participants who were randomized. The participants were analyzed according to the treatment they were randomized to receive, regardless of any errors of dosing. | |
| End point type | Primary |
| End point timeframe: | |
| Every 8 weeks from date of first dose treatment; every 12 weeks after 40 week assessment; at end of treatment visit until progressive disease. Duration is approximately 3 years | |

| End point values | Alisertib | Pralatrexate, or Romidepsin, or Gemcitabine | | |
|----------------------------------|-----------------|---------------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 138 | 133 | | |
| Units: days | | | | |
| median (confidence interval 95%) | 115 (83 to 174) | 104 (61 to 114) | | |

Statistical analyses

| | |
|-----------------------------------------|---------------------------------------------------------|
| Statistical analysis title | Statistical Analysis 1 |
| Comparison groups | Alisertib v Pralatrexate, or Romidepsin, or Gemcitabine |
| Number of subjects included in analysis | 271 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.177 |
| Method | Stratified Log Rank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.87 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.637 |
| upper limit | 1.178 |

Secondary: Overall Survival (OS)

| | |
|-----------------|-----------------------|
| End point title | Overall Survival (OS) |
|-----------------|-----------------------|

End point description:

OS was defined as the time from the date of randomization to the date of death. Participants without documentation of death were censored at the date last known to be alive. ITT population was defined as all participants who were randomized. The participants were analyzed according to the treatment they were randomized to receive, regardless of any errors of dosing.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Participants were followed for survival for 2 years from date of last participant off study treatment, or death, whichever occurs first. Contacts were every 4 months (Median follow-up 519 days in the alisertib arm and 586 days in the comparative arm)

| End point values | Alisertib | Pralatrexate, or Romidepsin, or Gemcitabine | | |
|----------------------------------|------------------|---------------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 138 | 133 | | |
| Units: days | | | | |
| median (confidence interval 95%) | 415 (263 to 514) | 367 (258 to 572) | | |

Statistical analyses

| | |
|-----------------------------------------|---------------------------------------------------------|
| Statistical analysis title | Statistical Analysis 1 |
| Comparison groups | Alisertib v Pralatrexate, or Romidepsin, or Gemcitabine |
| Number of subjects included in analysis | 271 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.338 |
| Method | Stratified Log-rank Test |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.98 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.707 |
| upper limit | 1.369 |

Secondary: Number of Participants with Treatment-Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

| | |
|-----------------|---------------------------------------------------------------------------------------------------------|
| End point title | Number of Participants with Treatment-Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs) |
|-----------------|---------------------------------------------------------------------------------------------------------|

End point description:

An Adverse Event (AE) is defined as any untoward medical occurrence in a clinical investigation participant administered a drug; it does not necessarily have to have a causal relationship with this treatment. A TEAE is defined as an adverse event with an onset that occurs after receiving study drug. A SAE is any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalization or prolongation of an existing hospitalization, results in persistent or significant disability or incapacity, is a congenital anomaly/ birth defect or is a medically important event. Safety population was defined as all participants who received at least 1 dose of alisertib, or one of the comparator drugs. Participants were analyzed according to the treatment actually received.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

First dose to 30 days after last dose of study drug or comparator (Up to 152 Weeks)

| End point values | Alisertib | Pralatrexate, or Romidepsin, or Gemcitabine | | |
|-----------------------------|-----------------|---------------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 137 | 127 | | |
| Units: participants | | | | |
| TEAE | 136 | 126 | | |
| SAE | 75 | 69 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Clinically Important Abnormal Laboratory Values Reported as AEs

| | |
|-----------------|---------------------------------------------------------------------------------------------|
| End point title | Number of Participants with Clinically Important Abnormal Laboratory Values Reported as AEs |
|-----------------|---------------------------------------------------------------------------------------------|

End point description:

Clinical laboratory tests included chemistry, hematology and urinalysis test. Clinically significant treatment-emergent laboratory abnormalities were reported by the investigator as TEAEs. Safety population was defined as all participants who received at least 1 dose of alisertib, or one of the comparator drugs. Participants were analyzed according to the treatment actually received.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

First dose to 30 days after last dose of study drug or comparator (Up to 152 Weeks)

| End point values | Alisertib | Pralatrexate, or Romidepsin, or Gemcitabine | | |
|---------------------------------------------|-----------------|---------------------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 137 | 127 | | |
| Units: participants | | | | |
| Neutrophil Count Decreased | 18 | 14 | | |
| White Blood Cell Count Decreased | 17 | 10 | | |
| Lymphocyte Count Decreased | 6 | 5 | | |
| Monocyte Count Decreased | 2 | 1 | | |
| Lymphocyte Count Increased | 1 | 0 | | |
| Monocyte Count Increased | 1 | 0 | | |
| White Blood Cell Count Increased | 1 | 0 | | |
| Platelet Count Decreased | 15 | 22 | | |
| Alanine Aminotransferase Increased | 8 | 11 | | |
| Aspartate Aminotransferase Increased | 5 | 11 | | |
| Gamma-glutamyltransferase Increased | 6 | 3 | | |
| Blood Bilirubin Increased | 2 | 1 | | |
| Hepatic Enzyme Increased | 2 | 0 | | |
| Liver Function Test Abnormal | 0 | 1 | | |
| Transaminases Increased | 0 | 1 | | |
| Blood Alkaline Phosphatase Increased | 9 | 7 | | |
| Blood Lactate Dehydrogenase Increased | 5 | 1 | | |
| Blood Creatinine Increased | 3 | 7 | | |
| Blood Creatinine Decreased | 0 | 1 | | |
| Blood Urea Increased | 1 | 0 | | |
| Blood Potassium Decreased | 1 | 4 | | |
| Blood Magnesium Decreased | 1 | 2 | | |
| Blood Bicarbonate Decreased | 0 | 1 | | |
| Blood Calcium Decreased | 0 | 1 | | |
| Blood Calcium Increased | 1 | 0 | | |
| Blood Phosphorus Decreased | 0 | 1 | | |
| Calcium Ionised Increased | 1 | 0 | | |
| Haemoglobin Decreased | 1 | 3 | | |
| Haematocrit Increased | 1 | 2 | | |
| Haematocrit Decreased | 1 | 0 | | |
| Coagulation Factor XIII Level Decreased | 1 | 0 | | |
| International Normalised Ratio Increased | 1 | 0 | | |
| Blood Albumin Decreased | 0 | 2 | | |
| Myocardial Necrosis Marker Increased | 1 | 0 | | |
| Troponin Increased | 0 | 1 | | |
| Blood Glucose Increased | 0 | 1 | | |
| Immunoglobulins Increased | 1 | 0 | | |
| Blood Uric Acid Increased | 1 | 0 | | |
| Enterovirus Test Positive | 0 | 1 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Clinically Important Vital Sign Measurements Reported as AEs

| | |
|-----------------|------------------------------------------------------------------------------------------|
| End point title | Number of Participants with Clinically Important Vital Sign Measurements Reported as AEs |
|-----------------|------------------------------------------------------------------------------------------|

End point description:

Vital signs included blood pressure, heart rate and temperature. Individual clinically significant changes in vital signs were reported by the investigator as TEAEs. Safety population was defined as all participants who received at least 1 dose of alisertib, or one of the comparator drugs. Participants were analyzed according to the treatment actually received.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

First dose to 30 days after last dose of study drug or comparator (Up to 152 Weeks)

| End point values | Alisertib | Pralatrexate, or Romidepsin, or Gemcitabine | | |
|-----------------------------|-----------------|---------------------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 137 | 127 | | |
| Units: participants | | | | |
| Heart Rate Increased | 1 | 0 | | |
| Body Temperature Increased | 0 | 1 | | |
| Hypotension | 4 | 6 | | |
| Orthostatic Hypotension | 2 | 1 | | |
| Hypertension | 5 | 7 | | |
| Pyrexia | 48 | 40 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Response (CR) Rate

| | |
|-----------------|-----------------------------|
| End point title | Complete Response (CR) Rate |
|-----------------|-----------------------------|

End point description:

Complete Response (CR) rate is defined as the percentage of participants with CR as assessed by the IRC using IWG criteria (2007 Cheson). CR= Disappearance of all evidence of disease. Response-evaluable population was defined as participants with peripheral T-cell lymphoma confirmed by an independent hematopathology central review, with measurable disease at baseline, who receive at least 1 dose of alisertib or the comparator drug, and 1 postbaseline response assessment of CR, PR, SD or PD by the independent radiology committee.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At the end of every 8 weeks from date of first dose treatment; every 12 weeks after 40 week assessment; at end of treatment visit until PD (approximately 3 years)

| End point values | Alisertib | Pralatrexate, or Romidepsin, or Gemcitabine | | |
|-----------------------------------|-----------------|---------------------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 102 | 92 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 18 (11 to 26) | 27 (18 to 37) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Disease Progression (TTP)

| | |
|-----------------|-----------------------------------|
| End point title | Time to Disease Progression (TTP) |
|-----------------|-----------------------------------|

End point description:

Time to Progression (TTP) was defined as the time from the date of randomization to the date of first documentation of PD/relapse. ITT population was defined as all participants who were randomized. The participants were analyzed according to the treatment they were randomized to receive, regardless of any errors of dosing.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At the end of every 8 weeks from date of first dose treatment; every 12 weeks after 40 week assessment; at end of treatment visit until progressive disease. Duration is approximately 3 years

| End point values | Alisertib | Pralatrexate, or Romidepsin, or Gemcitabine | | |
|----------------------------------|------------------|---------------------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 138 | 133 | | |
| Units: days | | | | |
| median (confidence interval 95%) | 162 (114 to 231) | 116 (101 to 227) | | |

Statistical analyses

| | |
|-----------------------------------------|---------------------------------------------------------|
| Statistical analysis title | Statistical Analysis 1 |
| Comparison groups | Alisertib v Pralatrexate, or Romidepsin, or Gemcitabine |
| Number of subjects included in analysis | 271 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[2] |
| P-value | = 0.362 |
| Method | Stratified Log Rank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.95 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.679 |
| upper limit | 1.329 |

Notes:

[2] - Hazard ratio was based on a stratified Cox's proportional hazard regression model with stratification factors: disease type, IPI Score and region with treatment as a factor in the model.

Secondary: Duration of Response (DOR)

| | |
|-----------------|----------------------------|
| End point title | Duration of Response (DOR) |
|-----------------|----------------------------|

End point description:

DOR was defined as the time from the date of first documentation of a PR or better to the date of first documentation of progressive disease (PD)/relapse for responders as assessed by the IRC using IWG criteria. Responders without documentation of PD/relapse were censored at the date of last response assessment that was stable disease (SD) or better. All responders in response-evaluable population defined as participants with peripheral T-cell lymphoma confirmed by independent hematopathology central review with measurable disease at baseline who receive at least 1 dose of alisertib or comparator drug and 1 postbaseline response assessment of CR, PR, SD or PD by independent radiology committee. 9999=NA (Not Available) Upper Limit Confidence Interval was not estimable due to the insufficient number of participants with the event.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At the end of every 8 weeks from date of first dose treatment; every 12 weeks after 40 week assessment; at end of treatment visit until progressive disease. Duration is approximately 3 years

| End point values | Alisertib | Pralatrexate, or Romidepsin, or Gemcitabine | | |
|----------------------------------|-------------------|---------------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 34 ^[3] | 41 ^[4] | | |
| Units: days | | | | |
| median (confidence interval 95%) | 225 (125 to 9999) | 172 (119 to 9999) | | |

Notes:

[3] - Here 9999=Upper CI is not estimable as upper boundary becomes nonsensical at certain value.

[4] - Here 9999=Upper CI is not estimable as upper boundary becomes nonsensical at certain value.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response

| | |
|-----------------|------------------|
| End point title | Time to Response |
|-----------------|------------------|

End point description:

Time to Response is defined as the time from the date of randomization to the date of first documentation of PR or better. All responders in response-evaluable population defined as participants with peripheral T-cell lymphoma confirmed by independent hematopathology central review with measurable disease at baseline who receive at least 1 dose of alisertib or comparator drug and 1 postbaseline response assessment of CR, PR, SD or PD by independent radiology committee.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At the end of every 8 weeks from date of first dose treatment; every 12 weeks after 40 week assessment; at end of treatment visit until progressive disease. Duration is approximately 3 years

| End point values | Alisertib | Pralatrexate, or Romidepsin, or Gemcitabine | | |
|----------------------------------|-----------------|---------------------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 34 | 41 | | |
| Units: days | | | | |
| median (confidence interval 95%) | 62 (57 to 67) | 64 (60 to 71) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Subsequent Antineoplastic Therapy

| | |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|
| End point title | Time to Subsequent Antineoplastic Therapy |
| End point description: | |
| Time to subsequent antineoplastic therapy was defined as the time from randomization to the first date of subsequent antineoplastic therapy (excluding transplant). Participants without subsequent antineoplastic therapy were censored at the date of death or last known to be alive. ITT population was defined as all participants who were randomized. The participants were analyzed according to the treatment they were randomized to receive, regardless of any errors of dosing. | |
| End point type | Secondary |
| End point timeframe: | |
| From date of last study drug to date of subsequent antineoplastic therapy, if required; approximately 3 years | |

| End point values | Alisertib | Pralatrexate, or Romidepsin, or Gemcitabine | | |
|----------------------------------|------------------|---------------------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 138 | 133 | | |
| Units: days | | | | |
| median (confidence interval 95%) | 336 (201 to 490) | 233 (144 to 429) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration-time Data to Contribute to Future Population Pharmacokinetics (PK) Analysis

| | |
|-----------------|-----------------------------------------------------------------------------------------------------------------|
| End point title | Plasma Concentration-time Data to Contribute to Future Population Pharmacokinetics (PK) Analysis ^[5] |
|-----------------|-----------------------------------------------------------------------------------------------------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Cycle 1, Days 1 and 7; Cycle 2, Day 8; Cycle 3, Day 8; Cycle 4, Day 8. Duration is approximately 4 months.

Notes:

[5] - 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: Only the Alisertib Arm is applicable to this Endpoint.

| | | | | |
|--------------------------------------|------------------|--|--|--|
| End point values | Alisertib | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 0 ^[6] | | | |
| Units: nM | | | | |
| arithmetic mean (standard deviation) | () | | | |

Notes:

[6] - This Outcome Measure was registered in error and is not a Primary or Secondary Outcome Measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Change Form Baseline in Reported Symptoms and Quality of Life (QoL) Assessment per Functional Assessment of Cancer Therapy-Lymphoma (FACT-LYM) for Functioning and Symptoms

| | |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Change Form Baseline in Reported Symptoms and Quality of Life (QoL) Assessment per Functional Assessment of Cancer Therapy-Lymphoma (FACT-LYM) for Functioning and Symptoms |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

The FACT-LYM includes the Functional Assessment of Cancer Therapy General Scale (FACT-G) and a 15-item lymphoma-specific subscale (LYM) over the past week. The FACT-G has 27 items that incorporate 4 scales including physical well-being (PWB; 7 items), social/family well-being (SWB, 7 items), emotional well-being (EWB; 6 items), and functional well-being (FWB; 7 items). The combined FACT-LYM instrument consists of a total of a 42 item questionnaire. Each question is answered on a 5- point scale of 0 (not at all) to 4 (very much) for a total possible score of 168. Higher scores indicate better well-being and a positive change from Baseline indicates improvement. ITT population was defined as all participants who were randomized. The participants were analyzed according to the treatment they were randomized to receive, regardless of any errors of dosing. Here, n= number of participants analyzed for this outcome measure.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and End of Treatment (EOT) (Up to 152 Weeks)

| | | | | |
|--------------------------------------|-----------------|---------------------------------------------|--|--|
| End point values | Alisertib | Pralatrexate, or Romidepsin, or Gemcitabine | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 138 | 133 | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Physical Well-Being, EOT (n= 81,70) | -2.4 (± 6.21) | -1.3 (± 5.27) | | |

| | | | | |
|------------------------------------------|---------------|---------------|--|--|
| Social/Family Well-Being, EOT (n=81, 69) | -0.3 (± 4.50) | 0.0 (± 4.44) | | |
| Emotional Well-Being, EOT (n=80, 67) | -1.4 (± 4.59) | -0.8 (± 3.93) | | |
| Functional Well-Being, EOT (n=80, 66) | -2.4 (± 5.40) | -0.3 (± 4.79) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First dose to 30 days after last dose of study drug or comparator (Up to 152 Weeks)

Adverse event reporting additional description:

At each visit investigator documented any occurrence of adverse events (AEs) and abnormal laboratory findings. Any event reported by the subject or observed by investigator was recorded, irrespective of relation to study treatment. AEs for arm "Gemcitabine or Pralatrexate or Romidepsin" were reported separately.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 15.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | Alisertib |
|-----------------------|-----------|

Reporting group description:

Alisertib 50 mg, enteric-coated tablet formulation, orally, twice daily for 7 consecutive days (Cycle Days 1-7) in a 21-day cycle (Up to 148 Weeks).

| | |
|-----------------------|-------------|
| Reporting group title | Gemcitabine |
|-----------------------|-------------|

Reporting group description:

Gemcitabine 1,000 mg/m² over 30 minutes, intravenously, on Days 1, 8, and 15 of a 28-day cycle until the absence of disease progression or unacceptable toxicity (Up to 32 Weeks).

| | |
|-----------------------|--------------|
| Reporting group title | Pralatrexate |
|-----------------------|--------------|

Reporting group description:

Pralatrexate 30 mg/m², intravenous (IV) push over 3 to 5 minutes, once weekly, for 6 weeks in 7-week cycles with concurrent vitamin B12 and folic acid supplementation. Cycles were repeated every 7-weeks provided the participant continued to benefit from and tolerate the therapy (Up to 115 Weeks).

| | |
|-----------------------|------------|
| Reporting group title | Romidepsin |
|-----------------------|------------|

Reporting group description:

Romidepsin 14 mg/m², intravenously over a 4-hour period, on Days 1, 8, and 15 of a 28-cycle. Cycles were repeated every 28 days provided the patient continued to benefit from and tolerate the therapy (Up to 30 Weeks).

| Serious adverse events | Alisertib | Gemcitabine | Pralatrexate |
|---------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 75 / 137 (54.74%) | 18 / 29 (62.07%) | 46 / 76 (60.53%) |
| number of deaths (all causes) | 11 | 5 | 8 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Peripheral T-cell lymphoma unspecified | Additional description: Five treatment-emergent deaths occurred during treatment and are not related, two with alisertib, one with gemcitabine, and two with romidepsin. | | |
| subjects affected / exposed | 2 / 137 (1.46%) | 2 / 29 (6.90%) | 1 / 76 (1.32%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| Lymphoma | Additional description: One treatment-emergent death occurred during | | |

| | treatment with alisertib and is not related. | | |
|-------------------------------------------------------|----------------------------------------------|----------------|----------------|
| subjects affected / exposed | 2 / 137 (1.46%) | 0 / 29 (0.00%) | 0 / 76 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Anaplastic large cell lymphoma T- and null-cell types | | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 0 / 76 (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 |
| Adenocarcinoma of colon | | | |
| subjects affected / exposed | 0 / 137 (0.00%) | 1 / 29 (3.45%) | 0 / 76 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Squamous cell carcinoma | | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 0 / 76 (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 |
| Plasma cell myeloma | | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 0 / 76 (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 |
| Myelodysplastic syndrome | | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 0 / 76 (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 |
| Adult T-cell lymphoma/leukaemia | | | |
| subjects affected / exposed | 0 / 137 (0.00%) | 0 / 29 (0.00%) | 1 / 76 (1.32%) |
| 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 | | | |
| Shock haemorrhagic | | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 0 / 76 (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 |

| | | | |
|------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|----------------|
| Thrombosis | | | |
| subjects affected / exposed | 0 / 137 (0.00%) | 0 / 29 (0.00%) | 1 / 76 (1.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 0 / 76 (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 |
| Orthostatic hypotension | | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 0 / 76 (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 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 12 / 137 (8.76%) | 6 / 29 (20.69%) | 6 / 76 (7.89%) |
| occurrences causally related to treatment / all | 3 / 12 | 3 / 6 | 3 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General physical health deterioration | Additional description: Three treatment-emergent deaths occurred during treatment with pralatrexate and are not related. | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 3 / 76 (3.95%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 3 |
| Multiple organ dysfunction syndrome | Additional description: Two treatment-emergent deaths occurred during treatment, one with alisertib, not related and one with pralatrexate, related. | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 1 / 76 (1.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 1 |
| Influenza like illness | | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 0 / 76 (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 |
| Fatigue | | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 1 / 76 (1.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|-------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|----------------|----------------|
| Hypothermia | | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 0 / 76 (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 |
| Catheter site phlebitis | | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 0 / 76 (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 |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 137 (0.00%) | 0 / 29 (0.00%) | 0 / 76 (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 |
| Pain | | | |
| subjects affected / exposed | 0 / 137 (0.00%) | 0 / 29 (0.00%) | 1 / 76 (1.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Adverse drug reaction | Additional description: One treatment-emergent death occurred during treatment with gemcitabine and is related. | | |
| subjects affected / exposed | 0 / 137 (0.00%) | 1 / 29 (3.45%) | 0 / 76 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 0 / 76 (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 |
| Anaphylactoid reaction | | | |
| subjects affected / exposed | 0 / 137 (0.00%) | 0 / 29 (0.00%) | 1 / 76 (1.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |

| | | | |
|-------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|----------------|----------------|
| subjects affected / exposed | 2 / 137 (1.46%) | 2 / 29 (6.90%) | 3 / 76 (3.95%) |
| occurrences causally related to treatment / all | 1 / 2 | 2 / 2 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory distress | | | |
| subjects affected / exposed | 0 / 137 (0.00%) | 0 / 29 (0.00%) | 0 / 76 (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 |
| Sleep apnoea syndrome | | | |
| subjects affected / exposed | 0 / 137 (0.00%) | 0 / 29 (0.00%) | 1 / 76 (1.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoxia | Additional description: Two treatment-emergent deaths occurred during treatment, one with alisertib and one with pralatrexate and are not related. | | |
| subjects affected / exposed | 2 / 137 (1.46%) | 0 / 29 (0.00%) | 2 / 76 (2.63%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 1 / 29 (3.45%) | 1 / 76 (1.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory failure | Additional description: One treatment-emergent death occurred during treatment with gemcitabine and is not related. | | |
| subjects affected / exposed | 0 / 137 (0.00%) | 1 / 29 (3.45%) | 2 / 76 (2.63%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Pleural effusion | Additional description: One treatment-emergent death occurred during treatment with pralatrexate and is not related. | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 1 / 76 (1.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 0 / 137 (0.00%) | 0 / 29 (0.00%) | 1 / 76 (1.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cough | | | |

| | | | |
|-------------------------------------------------|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 0 / 76 (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 |
| Hiccups | | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 0 / 76 (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 |
| Interstitial lung disease | | | |
| subjects affected / exposed | 0 / 137 (0.00%) | 0 / 29 (0.00%) | 1 / 76 (1.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 0 / 137 (0.00%) | 0 / 29 (0.00%) | 0 / 76 (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 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 0 / 76 (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 |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 0 / 76 (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 |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 0 / 76 (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 |
| Contusion | | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 0 / 76 (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 |

| | | | |
|------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|----------------|----------------|
| Spinal compression fracture subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 0 / 76 (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 |
| Cardiac disorders | | | |
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 1 / 76 (1.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 0 / 137 (0.00%) | 0 / 29 (0.00%) | 0 / 76 (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 |
| Cardiopulmonary failure | Additional description: One treatment-emergent death occurred during treatment with gemcitabine and is not related. | | |
| subjects affected / exposed | 0 / 137 (0.00%) | 1 / 29 (3.45%) | 0 / 76 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 137 (0.00%) | 0 / 29 (0.00%) | 1 / 76 (1.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sinus tachycardia | | | |
| subjects affected / exposed | 0 / 137 (0.00%) | 1 / 29 (3.45%) | 0 / 76 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bradycardia | | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 0 / 76 (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 |
| Tachycardia | | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 0 / 76 (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 |
| Atrioventricular block second degree | | | |

| | | | |
|-------------------------------------------------|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 0 / 76 (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 |
| Cardiomegaly | | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 0 / 76 (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 |
| Pericarditis | | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 0 / 76 (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 |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 137 (0.00%) | 0 / 29 (0.00%) | 1 / 76 (1.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 0 / 137 (0.00%) | 0 / 29 (0.00%) | 1 / 76 (1.32%) |
| 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 | 2 / 137 (1.46%) | 0 / 29 (0.00%) | 0 / 76 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Carotid artery aneurysm | | | |
| subjects affected / exposed | 0 / 137 (0.00%) | 1 / 29 (3.45%) | 0 / 76 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic encephalopathy | | | |
| subjects affected / exposed | 0 / 137 (0.00%) | 1 / 29 (3.45%) | 0 / 76 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Facial paralysis | | | |

| | | | |
|-------------------------------------------------|-------------------|----------------|----------------|
| subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 0 / 76 (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 |
| Presyncope | | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 0 / 76 (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 |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 24 / 137 (17.52%) | 1 / 29 (3.45%) | 1 / 76 (1.32%) |
| occurrences causally related to treatment / all | 21 / 27 | 1 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenia | | | |
| subjects affected / exposed | 2 / 137 (1.46%) | 0 / 29 (0.00%) | 1 / 76 (1.32%) |
| occurrences causally related to treatment / all | 2 / 7 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 7 / 137 (5.11%) | 1 / 29 (3.45%) | 4 / 76 (5.26%) |
| occurrences causally related to treatment / all | 6 / 8 | 1 / 1 | 4 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anaemia | | | |
| subjects affected / exposed | 7 / 137 (5.11%) | 0 / 29 (0.00%) | 2 / 76 (2.63%) |
| occurrences causally related to treatment / all | 4 / 9 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Microcytic anaemia | | | |
| subjects affected / exposed | 0 / 137 (0.00%) | 0 / 29 (0.00%) | 1 / 76 (1.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancytopenia | | | |
| subjects affected / exposed | 3 / 137 (2.19%) | 0 / 29 (0.00%) | 0 / 76 (0.00%) |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leukopenia | | | |

| | | | |
|---------------------------------------------------------------------------------------------------------------------|-----------------|----------------|------------------|
| subjects affected / exposed | 2 / 137 (1.46%) | 0 / 29 (0.00%) | 0 / 76 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 0 / 76 (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 |
| Gastrointestinal disorders | | | |
| Stomatitis | | | |
| subjects affected / exposed | 7 / 137 (5.11%) | 0 / 29 (0.00%) | 11 / 76 (14.47%) |
| occurrences causally related to treatment / all | 6 / 8 | 0 / 0 | 11 / 11 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 6 / 137 (4.38%) | 0 / 29 (0.00%) | 0 / 76 (0.00%) |
| occurrences causally related to treatment / all | 5 / 6 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 1 / 29 (3.45%) | 2 / 76 (2.63%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 2 / 137 (1.46%) | 0 / 29 (0.00%) | 1 / 76 (1.32%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 3 / 137 (2.19%) | 0 / 29 (0.00%) | 0 / 76 (0.00%) |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal perforation | | | |
| Additional description: One treatment-emergent death occurred during treatment with gemcitabine and is not related. | | | |
| subjects affected / exposed | 0 / 137 (0.00%) | 1 / 29 (3.45%) | 0 / 76 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Jejunal perforation | | | |

| | | | |
|-------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|----------------|----------------|
| subjects affected / exposed | 0 / 137 (0.00%) | 1 / 29 (3.45%) | 0 / 76 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 137 (0.00%) | 0 / 29 (0.00%) | 1 / 76 (1.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dysphagia | | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 0 / 76 (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 |
| Ileus | Additional description: One treatment-emergent death occurred during treatment with pralatrexate and is not related. | | |
| subjects affected / exposed | 0 / 137 (0.00%) | 0 / 29 (0.00%) | 1 / 76 (1.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Haematemesis | | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 0 / 76 (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 |
| Mouth haemorrhage | | | |
| subjects affected / exposed | 0 / 137 (0.00%) | 0 / 29 (0.00%) | 1 / 76 (1.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ascites | | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 0 / 76 (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 |
| Hepatobiliary disorders | | | |
| Drug-induced liver injury | | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 0 / 76 (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 |
| Hepatotoxicity | | | |

| | | | |
|-------------------------------------------------|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 137 (0.00%) | 1 / 29 (3.45%) | 0 / 76 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholangitis acute | | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 0 / 76 (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 |
| Cholestasis | | | |
| subjects affected / exposed | 0 / 137 (0.00%) | 0 / 29 (0.00%) | 1 / 76 (1.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic failure | | | |
| subjects affected / exposed | 0 / 137 (0.00%) | 0 / 29 (0.00%) | 1 / 76 (1.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Venoocclusive liver disease | | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 0 / 76 (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 |
| Skin and subcutaneous tissue disorders | | | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 2 / 137 (1.46%) | 0 / 29 (0.00%) | 0 / 76 (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 |
| Rash | | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 0 / 76 (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 |
| Dermatitis bullous | | | |
| subjects affected / exposed | 0 / 137 (0.00%) | 0 / 29 (0.00%) | 2 / 76 (2.63%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Toxic epidermal necrolysis | | | |

| | | | |
|-------------------------------------------------|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 137 (0.00%) | 0 / 29 (0.00%) | 1 / 76 (1.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain of skin | | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 0 / 76 (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 |
| Acute generalised exanthematous pustulosis | | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 0 / 76 (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 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 2 / 137 (1.46%) | 0 / 29 (0.00%) | 2 / 76 (2.63%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute prerenal failure | | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 0 / 76 (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 |
| Renal failure | | | |
| subjects affected / exposed | 0 / 137 (0.00%) | 1 / 29 (3.45%) | 0 / 76 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cystitis haemorrhagic | | | |
| subjects affected / exposed | 0 / 137 (0.00%) | 0 / 29 (0.00%) | 1 / 76 (1.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hydronephrosis | | | |
| subjects affected / exposed | 0 / 137 (0.00%) | 0 / 29 (0.00%) | 1 / 76 (1.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|-------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------|----------------|----------------|
| Back pain | | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 1 / 29 (3.45%) | 2 / 76 (2.63%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 137 (0.00%) | 1 / 29 (3.45%) | 0 / 76 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Compartment syndrome | | | |
| subjects affected / exposed | 0 / 137 (0.00%) | 0 / 29 (0.00%) | 1 / 76 (1.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Pneumonia | Additional description: One treatment-emergent death occurred during treatment with alisertib and is related. | | |
| subjects affected / exposed | 9 / 137 (6.57%) | 0 / 29 (0.00%) | 4 / 76 (5.26%) |
| occurrences causally related to treatment / all | 5 / 14 | 0 / 0 | 2 / 5 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Lung infection | | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 1 / 29 (3.45%) | 2 / 76 (2.63%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 137 (0.00%) | 0 / 29 (0.00%) | 1 / 76 (1.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | Additional description: One treatment-emergent death occurred during treatment with alisertib and is not related. | | |
| subjects affected / exposed | 2 / 137 (1.46%) | 0 / 29 (0.00%) | 2 / 76 (2.63%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Septic shock | Additional description: Four treatment-emergent deaths occurred during treatment with alisertib, two related and two not related. | | |
| subjects affected / exposed | 4 / 137 (2.92%) | 0 / 29 (0.00%) | 1 / 76 (1.32%) |
| occurrences causally related to treatment / all | 2 / 5 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 2 / 4 | 0 / 0 | 0 / 0 |

| | | | |
|-------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|----------------|----------------|
| Skin infection | Additional description: One treatment-emergent death occurred during treatment with pralatrexate and is not related. | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 2 / 76 (2.63%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Dermatitis infected | | | |
| subjects affected / exposed | 0 / 137 (0.00%) | 0 / 29 (0.00%) | 1 / 76 (1.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 1 / 76 (1.32%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epiglottitis | | | |
| subjects affected / exposed | 0 / 137 (0.00%) | 0 / 29 (0.00%) | 1 / 76 (1.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tonsillitis | | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 0 / 76 (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 |
| Cytomegalovirus infection | | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 1 / 76 (1.32%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cytomegalovirus chorioretinitis | | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 0 / 76 (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 | 0 / 137 (0.00%) | 1 / 29 (3.45%) | 0 / 76 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia bacterial | | | |

| | | | |
|-------------------------------------------------|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 0 / 76 (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 |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 0 / 76 (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 / 137 (0.73%) | 0 / 29 (0.00%) | 0 / 76 (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 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 2 / 137 (1.46%) | 0 / 29 (0.00%) | 0 / 76 (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 |
| Wound infection | | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 0 / 76 (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 |
| Pseudomonal sepsis | | | |
| subjects affected / exposed | 0 / 137 (0.00%) | 0 / 29 (0.00%) | 2 / 76 (2.63%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Erysipelas | | | |
| subjects affected / exposed | 2 / 137 (1.46%) | 0 / 29 (0.00%) | 0 / 76 (0.00%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 0 / 76 (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 |
| Meningitis aseptic | | | |

| | | | |
|-------------------------------------------------|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 137 (0.00%) | 1 / 29 (3.45%) | 0 / 76 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oral infection | | | |
| subjects affected / exposed | 0 / 137 (0.00%) | 0 / 29 (0.00%) | 1 / 76 (1.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia haemophilus | | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 0 / 76 (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 |
| Eczema herpeticum | | | |
| subjects affected / exposed | 0 / 137 (0.00%) | 0 / 29 (0.00%) | 1 / 76 (1.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Staphylococcal sepsis | | | |
| subjects affected / exposed | 0 / 137 (0.00%) | 0 / 29 (0.00%) | 0 / 76 (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 / 137 (1.46%) | 0 / 29 (0.00%) | 0 / 76 (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 |
| Staphylococcal skin infection | | | |
| subjects affected / exposed | 0 / 137 (0.00%) | 0 / 29 (0.00%) | 1 / 76 (1.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 0 / 76 (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 |
| Decreased appetite | | | |

| | | | |
|-------------------------------------------------|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 137 (0.00%) | 0 / 29 (0.00%) | 1 / 76 (1.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypophagia | | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 0 / 76 (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 |
| Electrolyte imbalance | | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 0 / 76 (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 |
| Tumour lysis syndrome | | | |
| subjects affected / exposed | 0 / 137 (0.00%) | 0 / 29 (0.00%) | 1 / 76 (1.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 0 / 76 (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 |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 0 / 76 (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 |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 0 / 76 (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 |

| Serious adverse events | Romidepsin | | |
|---------------------------------------------------|-----------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 6 / 22 (27.27%) | | |
| number of deaths (all causes) | 2 | | |
| number of deaths resulting from adverse events | | | |

| | | | |
|---------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|--|
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Peripheral T-cell lymphoma unspecified | Additional description: Five treatment-emergent deaths occurred during treatment and are not related, two with alisertib, one with gemcitabine, and two with romidepsin. | | |
| subjects affected / exposed | 2 / 22 (9.09%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Lymphoma | Additional description: One treatment-emergent death occurred during treatment with alisertib and is not related. | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Anaplastic large cell lymphoma T- and null-cell types | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Adenocarcinoma of colon | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Squamous cell carcinoma | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Plasma cell myeloma | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myelodysplastic syndrome | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Adult T-cell lymphoma/leukaemia | | | |

| | | | |
|------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|--|--|
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Shock haemorrhagic | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thrombosis | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Orthostatic hypotension | | | |
| subjects affected / exposed | 0 / 22 (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 | 1 / 22 (4.55%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General physical health deterioration | | | |
| Additional description: Three treatment-emergent deaths occurred during treatment with pralatrexate and are not related. | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Multiple organ dysfunction syndrome | | | |
| Additional description: Two treatment-emergent deaths occurred during treatment, one with alisertib, not related and one with pralatrexate, related. | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|-------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|--|--|
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fatigue | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypothermia | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Catheter site phlebitis | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pain | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Adverse drug reaction | Additional description: One treatment-emergent death occurred during treatment with gemcitabine and is related. | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Anaphylactoid reaction | | | |

| | | | |
|-------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|--|--|
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 2 / 22 (9.09%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory distress | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sleep apnoea syndrome | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypoxia | Additional description: Two treatment-emergent deaths occurred during treatment, one with alisertib and one with pralatrexate and are not related. | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory failure | Additional description: One treatment-emergent death occurred during treatment with gemcitabine and is not related. | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pleural effusion | Additional description: One treatment-emergent death occurred during treatment with pralatrexate and is not related. | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|-------------------------------------------------|----------------|--|--|
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cough | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hiccups | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Interstitial lung disease | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |

| | | | |
|-------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|--|--|
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Contusion | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Spinal compression fracture | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiopulmonary failure | Additional description: One treatment-emergent death occurred during treatment with gemcitabine and is not related. | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 2 / 22 (9.09%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sinus tachycardia | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bradycardia | | | |

| | | | |
|-------------------------------------------------|----------------|--|--|
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atrioventricular block second degree | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiomegaly | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pericarditis | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Syncope | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Carotid artery aneurysm | | | |

| | | | |
|-------------------------------------------------|----------------|--|--|
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatic encephalopathy | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Facial paralysis | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Presyncope | | | |
| subjects affected / exposed | 0 / 22 (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 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Microcytic anaemia | | | |

| | | | |
|-------------------------------------------------|----------------|--|--|
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pancytopenia | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nausea | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vomiting | | | |

| | | | |
|-------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|--|--|
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intestinal perforation | Additional description: One treatment-emergent death occurred during treatment with gemcitabine and is not related. | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Jejunal perforation | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ileus | Additional description: One treatment-emergent death occurred during treatment with pralatrexate and is not related. | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haematemesis | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Mouth haemorrhage | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ascites | | | |

| | | | |
|-------------------------------------------------|----------------|--|--|
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Drug-induced liver injury | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatotoxicity | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholangitis acute | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholestasis | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatic failure | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Venoocclusive liver disease | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rash | | | |

| | | | |
|-------------------------------------------------|----------------|--|--|
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dermatitis bullous | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Toxic epidermal necrolysis | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pain of skin | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acute generalised exanthematous pustulosis | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acute prerenal failure | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal failure | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cystitis haemorrhagic | | | |

| | | | |
|-------------------------------------------------|---------------------------------------------------------------------------------------------------------------|--|--|
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hydronephrosis | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Compartment syndrome | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Pneumonia | Additional description: One treatment-emergent death occurred during treatment with alisertib and is related. | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lung infection | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 22 (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 alisertib and is not related. | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Septic shock | Additional description: Four treatment-emergent deaths occurred during treatment with alisertib, two related and two not related. | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin infection | Additional description: One treatment-emergent death occurred during treatment with pralatrexate and is not related. | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dermatitis infected | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Epiglottitis | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tonsillitis | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cytomegalovirus infection | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cytomegalovirus chorioretinitis | | | |

| | | | | |
|-------------------------------------------------|----------------|--|--|--|
| subjects affected / exposed | 0 / 22 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cellulitis | | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonia bacterial | | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Clostridium difficile colitis | | | | |
| subjects affected / exposed | 0 / 22 (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 / 22 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Respiratory tract infection | | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Wound infection | | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pseudomonal sepsis | | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Erysipelas | | | | |

| | | | | |
|-------------------------------------------------|----------------|--|--|--|
| subjects affected / exposed | 0 / 22 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastroenteritis | | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Meningitis aseptic | | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Oral infection | | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonia haemophilus | | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Eczema herpeticum | | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Staphylococcal sepsis | | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Urinary tract infection | | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Staphylococcal skin infection | | | | |

| | | | |
|-------------------------------------------------|----------------|--|--|
| subjects affected / exposed | 0 / 22 (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 | 2 / 22 (9.09%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypophagia | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Electrolyte imbalance | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tumour lysis syndrome | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypoalbuminaemia | | | |

| | | | |
|-------------------------------------------------|----------------|--|--|
| subjects affected / exposed | 0 / 22 (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 | Gemcitabine | Pralatrexate |
|-------------------------------------------------------|--------------------|-------------------|------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 134 / 137 (97.81%) | 29 / 29 (100.00%) | 72 / 76 (94.74%) |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 5 / 137 (3.65%) | 2 / 29 (6.90%) | 2 / 76 (2.63%) |
| occurrences (all) | 5 | 2 | 2 |
| Hypotension | | | |
| subjects affected / exposed | 4 / 137 (2.92%) | 2 / 29 (6.90%) | 2 / 76 (2.63%) |
| occurrences (all) | 6 | 3 | 4 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 49 / 137 (35.77%) | 11 / 29 (37.93%) | 14 / 76 (18.42%) |
| occurrences (all) | 64 | 23 | 19 |
| Pyrexia | | | |
| subjects affected / exposed | 42 / 137 (30.66%) | 7 / 29 (24.14%) | 20 / 76 (26.32%) |
| occurrences (all) | 64 | 7 | 33 |
| Oedema peripheral | | | |
| subjects affected / exposed | 21 / 137 (15.33%) | 5 / 29 (17.24%) | 10 / 76 (13.16%) |
| occurrences (all) | 24 | 5 | 14 |
| Asthenia | | | |
| subjects affected / exposed | 24 / 137 (17.52%) | 2 / 29 (6.90%) | 10 / 76 (13.16%) |
| occurrences (all) | 46 | 2 | 15 |
| Chills | | | |
| subjects affected / exposed | 9 / 137 (6.57%) | 2 / 29 (6.90%) | 5 / 76 (6.58%) |
| occurrences (all) | 12 | 2 | 7 |
| Malaise | | | |
| subjects affected / exposed | 4 / 137 (2.92%) | 3 / 29 (10.34%) | 1 / 76 (1.32%) |
| occurrences (all) | 6 | 3 | 1 |
| Mucosal inflammation | | | |

| | | | |
|-------------------------------------------------|-------------------|-----------------|------------------|
| subjects affected / exposed | 3 / 137 (2.19%) | 1 / 29 (3.45%) | 5 / 76 (6.58%) |
| occurrences (all) | 4 | 1 | 5 |
| Peripheral swelling | | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 2 / 29 (6.90%) | 2 / 76 (2.63%) |
| occurrences (all) | 1 | 2 | 2 |
| Chest discomfort | | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 0 / 29 (0.00%) | 0 / 76 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 14 / 137 (10.22%) | 4 / 29 (13.79%) | 17 / 76 (22.37%) |
| occurrences (all) | 18 | 4 | 24 |
| Dyspnoea | | | |
| subjects affected / exposed | 12 / 137 (8.76%) | 4 / 29 (13.79%) | 8 / 76 (10.53%) |
| occurrences (all) | 16 | 4 | 9 |
| Epistaxis | | | |
| subjects affected / exposed | 5 / 137 (3.65%) | 1 / 29 (3.45%) | 11 / 76 (14.47%) |
| occurrences (all) | 5 | 1 | 17 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 6 / 137 (4.38%) | 1 / 29 (3.45%) | 6 / 76 (7.89%) |
| occurrences (all) | 9 | 1 | 6 |
| Productive cough | | | |
| subjects affected / exposed | 4 / 137 (2.92%) | 1 / 29 (3.45%) | 4 / 76 (5.26%) |
| occurrences (all) | 5 | 2 | 5 |
| Nasal congestion | | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 1 / 29 (3.45%) | 4 / 76 (5.26%) |
| occurrences (all) | 3 | 1 | 6 |
| Hypoxia | | | |
| subjects affected / exposed | 2 / 137 (1.46%) | 2 / 29 (6.90%) | 1 / 76 (1.32%) |
| occurrences (all) | 2 | 2 | 1 |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 12 / 137 (8.76%) | 2 / 29 (6.90%) | 3 / 76 (3.95%) |
| occurrences (all) | 16 | 2 | 3 |
| Anxiety | | | |

| | | | |
|---------------------------------------------------------------------------------------------|-------------------------|------------------------|-----------------------|
| subjects affected / exposed occurrences (all) | 5 / 137 (3.65%) 6 | 1 / 29 (3.45%) 1 | 4 / 76 (5.26%) 5 |
| Investigations | | | |
| Platelet count decreased subjects affected / exposed occurrences (all) | 16 / 137 (11.68%) 41 | 11 / 29 (37.93%) 38 | 6 / 76 (7.89%) 23 |
| Neutrophil count decreased subjects affected / exposed occurrences (all) | 18 / 137 (13.14%) 56 | 5 / 29 (17.24%) 9 | 5 / 76 (6.58%) 18 |
| White blood cell count decreased subjects affected / exposed occurrences (all) | 16 / 137 (11.68%) 33 | 5 / 29 (17.24%) 10 | 3 / 76 (3.95%) 11 |
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 8 / 137 (5.84%) 20 | 2 / 29 (6.90%) 2 | 9 / 76 (11.84%) 16 |
| Weight decreased subjects affected / exposed occurrences (all) | 12 / 137 (8.76%) 13 | 1 / 29 (3.45%) 1 | 6 / 76 (7.89%) 7 |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 5 / 137 (3.65%) 11 | 3 / 29 (10.34%) 3 | 8 / 76 (10.53%) 12 |
| Blood alkaline phosphatase increased subjects affected / exposed occurrences (all) | 9 / 137 (6.57%) 14 | 1 / 29 (3.45%) 1 | 5 / 76 (6.58%) 6 |
| Blood creatinine increased subjects affected / exposed occurrences (all) | 3 / 137 (2.19%) 3 | 3 / 29 (10.34%) 5 | 3 / 76 (3.95%) 4 |
| Haemoglobin decreased subjects affected / exposed occurrences (all) | 1 / 137 (0.73%) 1 | 2 / 29 (6.90%) 2 | 1 / 76 (1.32%) 2 |
| Cardiac disorders | | | |
| Tachycardia subjects affected / exposed occurrences (all) | 5 / 137 (3.65%) 5 | 0 / 29 (0.00%) 0 | 4 / 76 (5.26%) 4 |
| Angina pectoris | | | |

| | | | |
|--------------------------------------|-------------------|------------------|------------------|
| subjects affected / exposed | 0 / 137 (0.00%) | 0 / 29 (0.00%) | 0 / 76 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Palpitations | | | |
| subjects affected / exposed | 0 / 137 (0.00%) | 2 / 29 (6.90%) | 0 / 76 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 16 / 137 (11.68%) | 2 / 29 (6.90%) | 6 / 76 (7.89%) |
| occurrences (all) | 22 | 2 | 6 |
| Headache | | | |
| subjects affected / exposed | 15 / 137 (10.95%) | 2 / 29 (6.90%) | 5 / 76 (6.58%) |
| occurrences (all) | 22 | 3 | 7 |
| Somnolence | | | |
| subjects affected / exposed | 15 / 137 (10.95%) | 0 / 29 (0.00%) | 1 / 76 (1.32%) |
| occurrences (all) | 26 | 0 | 1 |
| Dysgeusia | | | |
| subjects affected / exposed | 3 / 137 (2.19%) | 0 / 29 (0.00%) | 2 / 76 (2.63%) |
| occurrences (all) | 3 | 0 | 2 |
| Disturbance in attention | | | |
| subjects affected / exposed | 2 / 137 (1.46%) | 0 / 29 (0.00%) | 0 / 76 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 74 / 137 (54.01%) | 7 / 29 (24.14%) | 30 / 76 (39.47%) |
| occurrences (all) | 166 | 12 | 46 |
| Neutropenia | | | |
| subjects affected / exposed | 66 / 137 (48.18%) | 11 / 29 (37.93%) | 21 / 76 (27.63%) |
| occurrences (all) | 351 | 25 | 43 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 51 / 137 (37.23%) | 12 / 29 (41.38%) | 29 / 76 (38.16%) |
| occurrences (all) | 140 | 26 | 82 |
| Leukopenia | | | |
| subjects affected / exposed | 39 / 137 (28.47%) | 6 / 29 (20.69%) | 6 / 76 (7.89%) |
| occurrences (all) | 115 | 12 | 18 |
| Lymphopenia | | | |

| | | | |
|-----------------------------|-------------------|-----------------|------------------|
| subjects affected / exposed | 14 / 137 (10.22%) | 2 / 29 (6.90%) | 5 / 76 (6.58%) |
| occurrences (all) | 29 | 2 | 15 |
| Febrile neutropenia | | | |
| subjects affected / exposed | 7 / 137 (5.11%) | 1 / 29 (3.45%) | 1 / 76 (1.32%) |
| occurrences (all) | 9 | 1 | 1 |
| Lymph node pain | | | |
| subjects affected / exposed | 1 / 137 (0.73%) | 2 / 29 (6.90%) | 1 / 76 (1.32%) |
| occurrences (all) | 1 | 3 | 1 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 61 / 137 (44.53%) | 5 / 29 (17.24%) | 18 / 76 (23.68%) |
| occurrences (all) | 139 | 5 | 37 |
| Stomatitis | | | |
| subjects affected / exposed | 42 / 137 (30.66%) | 0 / 29 (0.00%) | 48 / 76 (63.16%) |
| occurrences (all) | 99 | 0 | 114 |
| Nausea | | | |
| subjects affected / exposed | 35 / 137 (25.55%) | 7 / 29 (24.14%) | 23 / 76 (30.26%) |
| occurrences (all) | 48 | 7 | 35 |
| Constipation | | | |
| subjects affected / exposed | 17 / 137 (12.41%) | 6 / 29 (20.69%) | 20 / 76 (26.32%) |
| occurrences (all) | 18 | 6 | 25 |
| Vomiting | | | |
| subjects affected / exposed | 18 / 137 (13.14%) | 3 / 29 (10.34%) | 15 / 76 (19.74%) |
| occurrences (all) | 25 | 4 | 23 |
| Abdominal pain | | | |
| subjects affected / exposed | 16 / 137 (11.68%) | 1 / 29 (3.45%) | 7 / 76 (9.21%) |
| occurrences (all) | 40 | 1 | 13 |
| Dyspepsia | | | |
| subjects affected / exposed | 12 / 137 (8.76%) | 1 / 29 (3.45%) | 5 / 76 (6.58%) |
| occurrences (all) | 16 | 1 | 5 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 8 / 137 (5.84%) | 2 / 29 (6.90%) | 2 / 76 (2.63%) |
| occurrences (all) | 14 | 2 | 2 |
| Mouth ulceration | | | |
| subjects affected / exposed | 5 / 137 (3.65%) | 0 / 29 (0.00%) | 5 / 76 (6.58%) |
| occurrences (all) | 5 | 0 | 5 |

| | | | |
|-----------------------------------------------------------------------|-------------------------|----------------------|------------------------|
| Odynophagia subjects affected / exposed occurrences (all) | 2 / 137 (1.46%) 2 | 0 / 29 (0.00%) 0 | 5 / 76 (6.58%) 5 |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia subjects affected / exposed occurrences (all) | 43 / 137 (31.39%) 47 | 0 / 29 (0.00%) 0 | 1 / 76 (1.32%) 1 |
| Pruritus subjects affected / exposed occurrences (all) | 19 / 137 (13.87%) 31 | 1 / 29 (3.45%) 1 | 11 / 76 (14.47%) 14 |
| Rash subjects affected / exposed occurrences (all) | 5 / 137 (3.65%) 9 | 1 / 29 (3.45%) 1 | 7 / 76 (9.21%) 9 |
| Night sweats subjects affected / exposed occurrences (all) | 5 / 137 (3.65%) 5 | 2 / 29 (6.90%) 2 | 4 / 76 (5.26%) 5 |
| Skin lesion subjects affected / exposed occurrences (all) | 2 / 137 (1.46%) 5 | 2 / 29 (6.90%) 4 | 4 / 76 (5.26%) 8 |
| Skin ulcer subjects affected / exposed occurrences (all) | 3 / 137 (2.19%) 4 | 0 / 29 (0.00%) 0 | 4 / 76 (5.26%) 13 |
| Musculoskeletal and connective tissue disorders | | | |
| Pain in extremity subjects affected / exposed occurrences (all) | 15 / 137 (10.95%) 35 | 3 / 29 (10.34%) 4 | 6 / 76 (7.89%) 9 |
| Back pain subjects affected / exposed occurrences (all) | 12 / 137 (8.76%) 14 | 0 / 29 (0.00%) 0 | 6 / 76 (7.89%) 8 |
| Arthralgia subjects affected / exposed occurrences (all) | 8 / 137 (5.84%) 9 | 1 / 29 (3.45%) 1 | 3 / 76 (3.95%) 5 |
| Muscle spasms subjects affected / exposed occurrences (all) | 9 / 137 (6.57%) 11 | 2 / 29 (6.90%) 2 | 1 / 76 (1.32%) 1 |
| Musculoskeletal pain | | | |

| | | | |
|--------------------------------------------------|----------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 7 / 137 (5.11%) 8 | 0 / 29 (0.00%) 0 | 1 / 76 (1.32%) 3 |
| Infections and infestations | | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 14 / 137 (10.22%) | 3 / 29 (10.34%) | 3 / 76 (3.95%) |
| occurrences (all) | 21 | 5 | 4 |
| Influenza | | | |
| subjects affected / exposed | 8 / 137 (5.84%) | 1 / 29 (3.45%) | 3 / 76 (3.95%) |
| occurrences (all) | 13 | 2 | 3 |
| Conjunctivitis | | | |
| subjects affected / exposed | 4 / 137 (2.92%) | 0 / 29 (0.00%) | 7 / 76 (9.21%) |
| occurrences (all) | 4 | 0 | 9 |
| Pneumonia | | | |
| subjects affected / exposed | 4 / 137 (2.92%) | 0 / 29 (0.00%) | 5 / 76 (6.58%) |
| occurrences (all) | 4 | 0 | 5 |
| Sinusitis | | | |
| subjects affected / exposed | 5 / 137 (3.65%) | 0 / 29 (0.00%) | 2 / 76 (2.63%) |
| occurrences (all) | 7 | 0 | 2 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 4 / 137 (2.92%) | 2 / 29 (6.90%) | 3 / 76 (3.95%) |
| occurrences (all) | 4 | 2 | 3 |
| Skin infection | | | |
| subjects affected / exposed | 2 / 137 (1.46%) | 1 / 29 (3.45%) | 6 / 76 (7.89%) |
| occurrences (all) | 4 | 1 | 6 |
| Bronchitis | | | |
| subjects affected / exposed | 4 / 137 (2.92%) | 0 / 29 (0.00%) | 4 / 76 (5.26%) |
| occurrences (all) | 5 | 0 | 5 |
| Pharyngitis | | | |
| subjects affected / exposed | 3 / 137 (2.19%) | 0 / 29 (0.00%) | 4 / 76 (5.26%) |
| occurrences (all) | 4 | 0 | 4 |
| Oral herpes | | | |
| subjects affected / exposed | 3 / 137 (2.19%) | 3 / 29 (10.34%) | 0 / 76 (0.00%) |
| occurrences (all) | 3 | 4 | 0 |
| Mucosal infection | | | |
| subjects affected / exposed | 0 / 137 (0.00%) | 0 / 29 (0.00%) | 4 / 76 (5.26%) |
| occurrences (all) | 0 | 0 | 5 |

| | | | |
|------------------------------------|-------------------|----------------|------------------|
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 27 / 137 (19.71%) | 1 / 29 (3.45%) | 14 / 76 (18.42%) |
| occurrences (all) | 39 | 1 | 16 |
| Hypokalaemia | | | |
| subjects affected / exposed | 13 / 137 (9.49%) | 0 / 29 (0.00%) | 5 / 76 (6.58%) |
| occurrences (all) | 18 | 0 | 8 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 9 / 137 (6.57%) | 1 / 29 (3.45%) | 6 / 76 (7.89%) |
| occurrences (all) | 10 | 3 | 6 |
| Dehydration | | | |
| subjects affected / exposed | 4 / 137 (2.92%) | 0 / 29 (0.00%) | 7 / 76 (9.21%) |
| occurrences (all) | 4 | 0 | 9 |
| Hyponatraemia | | | |
| subjects affected / exposed | 3 / 137 (2.19%) | 0 / 29 (0.00%) | 4 / 76 (5.26%) |
| occurrences (all) | 3 | 0 | 5 |

| | | | |
|-------------------------------------------------------|------------------|--|--|
| Non-serious adverse events | Romidepsin | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 21 / 22 (95.45%) | | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 3 / 22 (13.64%) | | |
| occurrences (all) | 4 | | |
| Hypotension | | | |
| subjects affected / exposed | 2 / 22 (9.09%) | | |
| occurrences (all) | 2 | | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 6 / 22 (27.27%) | | |
| occurrences (all) | 9 | | |
| Pyrexia | | | |
| subjects affected / exposed | 3 / 22 (13.64%) | | |
| occurrences (all) | 4 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 5 / 22 (22.73%) | | |
| occurrences (all) | 6 | | |

| | | | |
|-------------------------------------------------|-----------------|--|--|
| Asthenia | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Chills | | | |
| subjects affected / exposed | 2 / 22 (9.09%) | | |
| occurrences (all) | 2 | | |
| Malaise | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | | |
| occurrences (all) | 1 | | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Peripheral swelling | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Chest discomfort | | | |
| subjects affected / exposed | 2 / 22 (9.09%) | | |
| occurrences (all) | 4 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 3 / 22 (13.64%) | | |
| occurrences (all) | 5 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 4 / 22 (18.18%) | | |
| occurrences (all) | 7 | | |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | | |
| occurrences (all) | 1 | | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | | |
| occurrences (all) | 1 | | |
| Productive cough | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nasal congestion | | | |

| | | | |
|--------------------------------------|-----------------|--|--|
| subjects affected / exposed | 2 / 22 (9.09%) | | |
| occurrences (all) | 2 | | |
| Hypoxia | | | |
| subjects affected / exposed | 2 / 22 (9.09%) | | |
| occurrences (all) | 2 | | |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | | |
| occurrences (all) | 1 | | |
| Anxiety | | | |
| subjects affected / exposed | 3 / 22 (13.64%) | | |
| occurrences (all) | 3 | | |
| Investigations | | | |
| Platelet count decreased | | | |
| subjects affected / exposed | 5 / 22 (22.73%) | | |
| occurrences (all) | 7 | | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 4 / 22 (18.18%) | | |
| occurrences (all) | 4 | | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 2 / 22 (9.09%) | | |
| occurrences (all) | 2 | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | | |
| occurrences (all) | 1 | | |
| Blood creatinine increased | | | |

| | | | |
|------------------------------------------------------------------------------|----------------------|--|--|
| subjects affected / exposed occurrences (all) | 2 / 22 (9.09%) 2 | | |
| Haemoglobin decreased subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | | |
| Cardiac disorders | | | |
| Tachycardia subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | | |
| Angina pectoris subjects affected / exposed occurrences (all) | 2 / 22 (9.09%) 2 | | |
| Palpitations subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | | |
| Nervous system disorders | | | |
| Dizziness subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | | |
| Headache subjects affected / exposed occurrences (all) | 2 / 22 (9.09%) 2 | | |
| Somnolence subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | | |
| Dysgeusia subjects affected / exposed occurrences (all) | 4 / 22 (18.18%) 5 | | |
| Disturbance in attention subjects affected / exposed occurrences (all) | 2 / 22 (9.09%) 2 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 6 / 22 (27.27%) 8 | | |
| Neutropenia | | | |

| | | | |
|-----------------------------|------------------|--|--|
| subjects affected / exposed | 7 / 22 (31.82%) | | |
| occurrences (all) | 7 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 7 / 22 (31.82%) | | |
| occurrences (all) | 17 | | |
| Leukopenia | | | |
| subjects affected / exposed | 2 / 22 (9.09%) | | |
| occurrences (all) | 3 | | |
| Lymphopenia | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | | |
| occurrences (all) | 1 | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Lymph node pain | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 10 / 22 (45.45%) | | |
| occurrences (all) | 12 | | |
| Stomatitis | | | |
| subjects affected / exposed | 2 / 22 (9.09%) | | |
| occurrences (all) | 3 | | |
| Nausea | | | |
| subjects affected / exposed | 15 / 22 (68.18%) | | |
| occurrences (all) | 17 | | |
| Constipation | | | |
| subjects affected / exposed | 3 / 22 (13.64%) | | |
| occurrences (all) | 5 | | |
| Vomiting | | | |
| subjects affected / exposed | 4 / 22 (18.18%) | | |
| occurrences (all) | 5 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 22 (9.09%) | | |
| occurrences (all) | 2 | | |

| | | | |
|--------------------------------------------------------------------------|----------------------|--|--|
| Dyspepsia subjects affected / exposed occurrences (all) | 2 / 22 (9.09%) 2 | | |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | | |
| Mouth ulceration subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | | |
| Odynophagia subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | | |
| Pruritus subjects affected / exposed occurrences (all) | 5 / 22 (22.73%) 5 | | |
| Rash subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | | |
| Night sweats subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | | |
| Skin lesion subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | | |
| Skin ulcer subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Pain in extremity subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | | |
| Back pain | | | |

| | | | |
|-----------------------------------------|-----------------|--|--|
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | | |
| occurrences (all) | 1 | | |
| Muscle spasms | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | | |
| occurrences (all) | 1 | | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Infections and infestations | | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | | |
| occurrences (all) | 1 | | |
| Influenza | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Conjunctivitis | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | | |
| occurrences (all) | 1 | | |
| Sinusitis | | | |
| subjects affected / exposed | 3 / 22 (13.64%) | | |
| occurrences (all) | 3 | | |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | | |
| occurrences (all) | 1 | | |
| Skin infection | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |

| | | | |
|------------------------------------|-----------------|--|--|
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Oral herpes | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Mucosal infection | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 9 / 22 (40.91%) | | |
| occurrences (all) | 11 | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 2 / 22 (9.09%) | | |
| occurrences (all) | 2 | | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dehydration | | | |
| subjects affected / exposed | 2 / 22 (9.09%) | | |
| occurrences (all) | 2 | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | | |
| occurrences (all) | 1 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 11 October 2012 | <p>Protocol Amendments 3 and 4 were developed in parallel for all countries and for those where romidepsin use was not permitted. The key purposes of Amendments 3 and 4 were to:</p> <ol style="list-style-type: none">1. Remove the NPO (nothing by mouth) requirements around alisertib administration.2. Update that OS would be analyzed twice, first at the final analysis, and then again after approximately 80% of all patients in the ITT population had death events, which was anticipated to be approximately 42 months after the last patient in.3. Add that HIV testing was to be performed during screening, only where required by local regulations.4. Remove the eligibility criterion excluding patients with albumin below the lower limit of normal.5. Remove the censoring method from the protocol and indicate that details of censoring would be described in the SAP.6. Change the analysis of ORR at the second interim analysis from stratified CMH test to unstratified CMH test because the sample size might be too small for a stratified CMH test.7. Confirm that up to a maximum of 354 patients (ie, not response-evaluable patients) would be enrolled to reach a maximum of 261 PFS events (Amendment 3).8. Specify that patients with CD30+ ALCL ALK+ disease are expected to have received anti- CD30+ targeted therapy, where approved, prior to entering this study.9. Remove blastic NK lymphoma as a PTCL subtype included in this study.10. Add the EQ5D-3L as a QOL assessment during OS follow-up.11. Remove statements regarding the use of flumazenil and CNS stimulants (such as modafinil or methylphenidate).12. Update the Clinical Pharmacokinetics and Clinical Experience sections to align with the current Investigator's Brochure.13. Update the anticipated number of sites and countries participating in this study.14. Delete redundant SAE reporting language and update reporting period for SAEs to Millennium from 1 working day to 24 hours.15. Permitted food at dosing and clarified that Chesson 2007 guidance to be followed |
| 11 March 2014 | <p>Protocol Amendments 5 and 6 were developed in parallel for all countries and for those where romidepsin use was not permitted. The key purposes of Amendments 5 and 6 were to:</p> <ol style="list-style-type: none">1. Indicate a change in the SAE reporting center from PPD, Inc. to Cognizant.2. Update language to current company standards and remove text regarding the start of antineoplastic or anticancer therapy as it related to follow-up of AEs.3. Made key secondary endpoint OS (not OS and CR rate) |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported