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/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).

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/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).	

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	61.1	61.4	
standard deviation	± 12.69	± 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

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/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).

Reporting group title	Pralatrexate

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).

Reporting group title	Romidepsin

Reporting group description:

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).

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	5 / 137 (3.65%)	1 / 29 (3.45%)	4 / 76 (5.26%)
occurrences (all)	6	1	5
Investigations			
Platelet count decreased			
subjects affected / exposed	16 / 137 (11.68%)	11 / 29 (37.93%)	6 / 76 (7.89%)
occurrences (all)	41	38	23
Neutrophil count decreased			
subjects affected / exposed	18 / 137 (13.14%)	5 / 29 (17.24%)	5 / 76 (6.58%)
occurrences (all)	56	9	18
White blood cell count decreased			
subjects affected / exposed	16 / 137 (11.68%)	5 / 29 (17.24%)	3 / 76 (3.95%)
occurrences (all)	33	10	11
Alanine aminotransferase increased			
subjects affected / exposed	8 / 137 (5.84%)	2 / 29 (6.90%)	9 / 76 (11.84%)
occurrences (all)	20	2	16
Weight decreased			
subjects affected / exposed	12 / 137 (8.76%)	1 / 29 (3.45%)	6 / 76 (7.89%)
occurrences (all)	13	1	7
Aspartate aminotransferase increased			
subjects affected / exposed	5 / 137 (3.65%)	3 / 29 (10.34%)	8 / 76 (10.53%)
occurrences (all)	11	3	12
Blood alkaline phosphatase increased			
subjects affected / exposed	9 / 137 (6.57%)	1 / 29 (3.45%)	5 / 76 (6.58%)
occurrences (all)	14	1	6
Blood creatinine increased			
subjects affected / exposed	3 / 137 (2.19%)	3 / 29 (10.34%)	3 / 76 (3.95%)
occurrences (all)	3	5	4
Haemoglobin decreased			
subjects affected / exposed	1 / 137 (0.73%)	2 / 29 (6.90%)	1 / 76 (1.32%)
occurrences (all)	1	2	2
Cardiac disorders			
Tachycardia			
subjects affected / exposed	5 / 137 (3.65%)	0 / 29 (0.00%)	4 / 76 (5.26%)
occurrences (all)	5	0	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	2 / 137 (1.46%)	0 / 29 (0.00%)	5 / 76 (6.58%)
occurrences (all)	2	0	5
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	43 / 137 (31.39%)	0 / 29 (0.00%)	1 / 76 (1.32%)
occurrences (all)	47	0	1
Pruritus			
subjects affected / exposed	19 / 137 (13.87%)	1 / 29 (3.45%)	11 / 76 (14.47%)
occurrences (all)	31	1	14
Rash			
subjects affected / exposed	5 / 137 (3.65%)	1 / 29 (3.45%)	7 / 76 (9.21%)
occurrences (all)	9	1	9
Night sweats			
subjects affected / exposed	5 / 137 (3.65%)	2 / 29 (6.90%)	4 / 76 (5.26%)
occurrences (all)	5	2	5
Skin lesion			
subjects affected / exposed	2 / 137 (1.46%)	2 / 29 (6.90%)	4 / 76 (5.26%)
occurrences (all)	5	4	8
Skin ulcer			
subjects affected / exposed	3 / 137 (2.19%)	0 / 29 (0.00%)	4 / 76 (5.26%)
occurrences (all)	4	0	13
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	15 / 137 (10.95%)	3 / 29 (10.34%)	6 / 76 (7.89%)
occurrences (all)	35	4	9
Back pain			
subjects affected / exposed	12 / 137 (8.76%)	0 / 29 (0.00%)	6 / 76 (7.89%)
occurrences (all)	14	0	8
Arthralgia			
subjects affected / exposed	8 / 137 (5.84%)	1 / 29 (3.45%)	3 / 76 (3.95%)
occurrences (all)	9	1	5
Muscle spasms			
subjects affected / exposed	9 / 137 (6.57%)	2 / 29 (6.90%)	1 / 76 (1.32%)
occurrences (all)	11	2	1
Musculoskeletal pain			

subjects affected / exposed	7 / 137 (5.11%)	0 / 29 (0.00%)	1 / 76 (1.32%)
occurrences (all)	8	0	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	2 / 22 (9.09%)		
occurrences (all)	2		
Haemoglobin decreased			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Angina pectoris			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Palpitations			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Somnolence			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Dysgeusia			
subjects affected / exposed	4 / 22 (18.18%)		
occurrences (all)	5		
Disturbance in attention			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 22 (27.27%)		
occurrences (all)	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) Abdominal pain upper subjects affected / exposed occurrences (all) Mouth ulceration subjects affected / exposed occurrences (all) Odynophagia subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2 0 / 22 (0.00%) 0 0 / 22 (0.00%) 0 0 / 22 (0.00%) 0		
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all) Night sweats subjects affected / exposed occurrences (all) Skin lesion subjects affected / exposed occurrences (all) Skin ulcer subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0 5 / 22 (22.73%) 5 1 / 22 (4.55%) 1 1 / 22 (4.55%) 1 1 / 22 (4.55%) 1 0 / 22 (0.00%) 0		
Musculoskeletal and connective tissue disorders Pain in extremity subjects affected / exposed occurrences (all) Back pain	1 / 22 (4.55%) 1		

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 October 2012	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: 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	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: 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