Clinical trial results:
A Phase 2 Trial of MLN8237, an Oral Aurora A Kinase Inhibitor, in Adult Patients with Acute Myelogenous Leukemia and High-Grade Myelodysplastic Syndrome

Summary

EudraCT number	2008-006977-34
Trial protocol	FR
Global end of trial date	04 July 2011

Results information

Result version number	v1
This version publication date	21 January 2018
First version publication date	30 December 2016
Summary attachment (see zip file)	Summary Results (C14005-RDS-2012-04-10.pdf)

Trial information

Trial identification

Sponsor protocol code	C14005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00830518
WHO universal trial number (UTN)	U1111-1187-6616

Notes:

Sponsors

Sponsor organisation name	Takeda Oncology
Sponsor organisation address	40 Landsdowne Street, Cambridge, MA, United States, USA 02139
Public contact	Medical Director,Clinical Science, Takeda Oncology, +1 844-662-8532, GlobalOncologyMedinfo@takeda.com
Scientific contact	Medical Director,Clinical Science, Takeda Oncology, +1 844-662-8532, GlobalOncologyMedinfo@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	04 July 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 July 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To estimate antitumor activity of MLN8237 as measured by response rate in participants with Acute Myelogenous Leukemia (AML) and High-Grade Myelodysplastic Syndrome (MDS)

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	10 February 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 42
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	France: 13
Worldwide total number of subjects	57
EEA total number of subjects	13

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)	7
From 65 to 84 years	49
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 19 investigative sites in France, Canada and the United States from 10 February 2009 to 04 July 2011.

Pre-assignment

Screening details:

Participants with a diagnosis of acute myelogenous leukemia or myelodysplastic syndrome received 50 mg alisertib twice daily for 7 days in 21 day cycles. Results are reported according to lymphoma disease subtypes: acute myelogenous leukemia and myelodysplastic syndrome.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Alisertib 50 mg (Acute myeloid leukemia)

Arm description:

Participants with acute myeloid leukemia received alisertib 50 mg, capsules, orally, twice daily for 7 days, followed by 14-day washout period, in 21-day cycles until disease progression or unacceptable treatment-related toxicity (Up to 26 Cycles).

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

Dosage and administration details:

Participants with acute myeloid leukemia received alisertib 50 mg, capsules, orally, twice daily for 7 days, followed by 14-day washout period, in 21-day cycles until disease progression or unacceptable treatment-related toxicity (Up to 26 Cycles).

Arm title	Alisertib 50 mg (Myelodysplastic syndrome)

Arm description:

Participants with myelodysplastic syndrome received alisertib 50 mg, capsules, orally, twice daily for 7 days, followed by 14-day washout period, in 21-day cycles until disease progression or unacceptable treatment-related toxicity (Up to 6 Cycles).

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

Dosage and administration details:

Participants with myelodysplastic syndrome received alisertib 50 mg, capsules, orally, twice daily for 7 days, followed by 14-day washout period, in 21-day cycles until disease progression or unacceptable treatment-related toxicity (Up to 6 Cycles).

Number of subjects in period 1	Alisertib 50 mg (Acute myeloid leukemia)	Alisertib 50 mg (Myelodysplastic syndrome)
Started	46	11
Completed	0	0
Not completed	46	11
Adverse event, non-fatal	14	1
Progressive Disease	18	8
Withdrawal by Patient	2	-
Symptomatic Deterioration	4	1
Reason not Specified	8	1

Baseline characteristics

Reporting groups	
Reporting group title	Alisertib 50 mg (Acute myeloid leukemia)
Reporting group description:	
Participants with acute myeloid leukemia received alisertib 50 mg, capsules, orally, twice daily for 7 days, followed by 14-day washout period, in 21-day cycles until disease progression or unacceptable treatment-related toxicity (Up to 26 Cycles).	
Reporting group title	Alisertib 50 mg (Myelodysplastic syndrome)
Reporting group description:	
Participants with myelodysplastic syndrome received alisertib 50 mg, capsules, orally, twice daily for 7 days, followed by 14-day washout period, in 21-day cycles until disease progression or unacceptable treatment-related toxicity (Up to 6 Cycles).	

Reporting group values	Alisertib 50 mg (Acute myeloid leukemia)	Alisertib 50 mg (Myelodysplastic syndrome)	Total
Number of subjects	46	11	57
Age Categorical Units: Subjects			
<60 years	4	2	6
≥60 years	42	9	51
Age Continuous Units: years			
arithmetic mean	71.9	69.5	
standard deviation	± 7.41	± 12.50	-
Gender, Male/Female Units: Subjects			
Female	22	3	25
Male	24	8	32
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino	2	0	2
Not Hispanic or Latino	34	9	43
Not Reported	10	2	12
Region of Enrollment Units: Subjects			
United States	33	9	42
France	11	2	13
Canada	2	0	2
Race/Ethnicity, Customized Units: Subjects			
White	36	10	46
Black or African American	3	0	3
Asian	1	0	1
Not Reported	6	1	7
Eastern Cooperative Oncology Group (ECOG) Performance Status			
ECOG performance is defined as: 0=Normal activity (fully active, able to carry on all predisease performance without restriction); 1=Symptoms but ambulatory (restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature); 2=In bed <50% of the time (ambulatory and capable of all self-care, but unable to carry out any work activities.			

Units: Subjects			
ECOG Performance Status=0	9	3	12
ECOG Performance Status=1	29	8	37
ECOG Performance Status=2	8	0	8
Study Specific Characteristic | Height			
Baseline height data is available for n=36,10, respectively.			
Units: cm			
arithmetic mean	165.8	171.4	
standard deviation	± 8.35	± 9.98	-
Study Specific Characteristic | Weight			
Baseline weight data is available for n=45,11, respectively.			
Units: kg			
arithmetic mean	73.7	80.4	
standard deviation	± 13.80	± 17.27	-
Study Specific Characteristic | Baseline Body Surface Area (BSA)			
Baseline BSA data is available for n=36,10, respectively.			
Units: m^2			
arithmetic mean	1.83	1.94	
standard deviation	± 0.203	± 0.262	-
Study Specific Characteristic | Years Since Initial Diagnosis			
Units: years			
arithmetic mean	0.65	0.82	
standard deviation	± 0.793	± 0.780	-

End points

End points reporting groups

Reporting group title	Alisertib 50 mg (Acute myeloid leukemia)

Reporting group description:

Participants with acute myeloid leukemia received alisertib 50 mg, capsules, orally, twice daily for 7 days, followed by 14-day washout period, in 21-day cycles until disease progression or unacceptable treatment-related toxicity (Up to 26 Cycles).

Reporting group title	Alisertib 50 mg (Myelodysplastic syndrome)

Reporting group description:

Participants with myelodysplastic syndrome received alisertib 50 mg, capsules, orally, twice daily for 7 days, followed by 14-day washout period, in 21-day cycles until disease progression or unacceptable treatment-related toxicity (Up to 6 Cycles).

Primary: Best Overall Response Rate (ORR) Based on Investigator's Assessment

End point title	Best Overall Response Rate (ORR) Based on Investigator's Assessment[1]

End point description:

Best ORR:number of participants with complete remission(CR)/partial remission(PR) assessed by Investigator using modified AML/MDS International Working Group Criteria.AML:CR=neutrophils>1*10^9/L,platelets>100*10^9/L,bone marrow blasts(BMB)<5%,transfusion independent,no extramedullary disease(EMD);CRi=BMB<5%,transfusion independent,no EMD;PR=neutrophils>1*10^9/L,platelets>100*10^9/L, BMB>50% decrease(dec.)and 5% to 25%,blasts<5% with Auer rods;PRi=BMB>50%dec.and 5%-25%.MDS:CR=bone marrow:≤5%myeloblasts with normal maturation,peripheral blood:hemoglobin ≥11g/dL,platelets ≥100*10^9/L,neutrophils≥1.0*10^9/L,blasts0%;PR=all CR criteria if abnormal before treatment except:BMB dec.by ≥50% over pretreatment but still>5%;PRi=BMB dec.by ≥50% over pretreatment but still >5%;Marrow CR=bone marrow:≤5% myeloblasts and dec.by ≥50% over pretreatment,peripheral blood hematologic improvement responses noted. (Response-Evaluable

End point type	Primary

End point timeframe:

Baseline and every 2 cycles up to Cycle 16 (up to Month 12), from Cycle 17 every 4 cycles until disease progression, after end of treatment every 12 weeks for up to 12 Months (Approximately 2.4 years)

Notes:

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

End point values	Alisertib 50 mg (Acute myeloid leukemia)	Alisertib 50 mg (Myelodysplastic syndrome)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	10		
Units: participants				
CR + PR	6	0		
Complete Remission (CR + CRi + Marrow CRi)	1	0		
Partial Remission (PR + PRi)	5	0		
Stable Disease as Best Response	17	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

PFS is defined as the time from the date of first study drug administration to the date of first documented progressive disease (PD) or death.Response-Evaluable Population included all participants who received at least 1 dose of alisertib and had at least 1 post-baseline response assessment. For a participant that has not progressed and has not died, PFS is censored at the last response assessment that is SD or better.

End point type	Secondary

End point timeframe:

Baseline and every 2 cycles up to Cycle 16 (up to Month 12), from Cycle 17 every 4 cycles until disease progression, after end of treatment every 12 weeks for up to 12 Months (Approximately 2.4 years)

End point values	Alisertib 50 mg (Acute myeloid leukemia)	Alisertib 50 mg (Myelodysplastic syndrome)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	10		
Units: days				
median (confidence interval 95%)	55.0 (47.0 to 67.0)	38.0 (35.0 to 113.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

Duration of response is defined as the time from the date of first documentation of a response to the date of first documented PD. Response--Evaluable Population included all participants who had measurable disease, received at least 1 dose of alisertib, and had at least 1 post baseline response assessment. All responders were evaluated in this outcome measure. For a participant that has not progressed, DOR is censored at the last response assessment that is SD or better.

End point type	Secondary

End point timeframe:

Baseline and every 2 cycles up to Cycle 16 (up to Month 12), from Cycle 17 every 4 cycles until disease progression, after end of treatment every 12 weeks for up to 12 Months (Approximately 2.4 years)

End point values	Alisertib 50 mg (Acute myeloid leukemia)	Alisertib 50 mg (Myelodysplastic syndrome)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	0[2]		
Units: days				
median (confidence interval 95%)	409.0 (57.0 to 596.0)	(to)		

Notes:

[2] - No participants with response.

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Hematologic Improvement (HI) Response for Myelodysplastic Syndrome Based on Investigator Assessment

End point title	Best Overall Hematologic Improvement (HI) Response for Myelodysplastic Syndrome Based on Investigator Assessment[3]

End point description:

Best overall HI response:percentage of participants with response as assessed by Investigator based on IWG criteria:1)Erythroid response (pretreatment,<11 g/dL):hemoglobin(Hgb) increase(inc.) by ≥1.5 g/dL,relevant reduction of units of red blood cell (RBC) transfusions by absolute number of at least 4 RBC transfusions/8 weeks compared to pretreatment transfusion number in previous 8 weeks.Only RBC transfusions given for Hgb of ≤9.0 g/dL pretreatment will count in RBC transfusion response evaluation.2)Platelet response(pretreatment<100*10^9/L):Absolute inc. of ≥30*10^9/L for participants starting:>20*10^9/L platelets, inc.<20*10^9/L to >20*10^9/L by at least 100%.3)Neutrophil response(pretreatment,<1.0*10^9/L):At least 100% inc. and an absolute inc. >0.5*10^9/L.4)Progression or relapse after HI:At least 1 of following: 50% decrement from maximum response levels in granulocytes or platelets, or reduction in Hgb by ≥1.5g/dL,or transfusion dependence.

End point type	Secondary

End point timeframe:

Baseline and every 2 cycles up to Cycle 16 (up to Month 12), from Cycle 17 every 4 cycles until disease progression, after end of treatment every 12 weeks for up to 12 Months (Approximately 2.4 years)

Notes:

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

End point values	Alisertib 50 mg (Myelodysplastic syndrome)			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: percentage of participants				
Erythroid Response	0			
Platelet Response	0			
Neutrophil Response	0			
Progression or Relapse	0			
Not Available	91			
Unable to Assess	9			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events (AEs), Serious Adverse Events (SAEs) and Deaths

End point title	Number of Participants with Adverse Events (AEs), Serious Adverse Events (SAEs) and Deaths

End point description:

An AE is defined as any untoward medical occurrence in a participant administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. A serious adverse event (SAE) is defined as 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. Relationship of each AE to study drug was determined by the Investigator.Safety population was defined as all participants who received any amount of alisertib.

End point type	Secondary

End point timeframe:

First dose of study drug to 30 days after last dose (Up to 18.9 months)

End point values	Alisertib 50 mg (Acute myeloid leukemia)	Alisertib 50 mg (Myelodysplastic syndrome)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	11		
Units: participants				
AE	46	11		
SAE	36	8		
Deaths	20	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Abnormal Vital Signs Reported as Treatment-Emergent Adverse Events

End point title	Number of Participants with Abnormal Vital Signs Reported as Treatment-Emergent Adverse Events

End point description:

Vital signs measurements (blood pressure, heart rate, and oral temperature) were obtained throughout the study. A treatment-emergent adverse event (TEAE) is defined as an adverse event with an onset that occurs after receiving study drug.Safety population was defined as all participants who received any amount of alisertib.

End point type	Secondary

End point timeframe:

First dose of study drug to 30 days after last dose (Up to 18.9 months)

End point values	Alisertib 50 mg (Acute myeloid leukemia)	Alisertib 50 mg (Myelodysplastic syndrome)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	11		
Units: participants				
Dyspnoea	12	2		
Pyrexia	10	2		
Hypotension	8	0		
Atrial fibrillation	4	1		
Tachycardia	3	0		
Dyspnoea exertional	2	1		
Hypertension	1	1		
Supraventricular tachycardia	2	0		
Weight decreased	2	0		
Tachypnoea	1	0		
Hyperthermia	1	0		
Hypothermia	1	0		
Bradycardia	0	1		
Ventricular tachycardia	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Abnormal Laboratory Values reported as Treatment-Emergent Adverse Events

End point title	Number of Participants with Abnormal Laboratory Values reported as Treatment-Emergent Adverse Events

End point description:

Abnormal Laboratory Values for Chemistry or Hematology tests that were assessed by the investigator to be Grade 3 or higher using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE). Grade 3=severe, Grade 4=life threatening or disabling and Grade 5=Death. A treatment--emergent adverse event (TEAE) is defined as an adverse event with an onset that occurs after receiving study drug.Safety population was defined as all participants who received any amount of alisertib.

End point type	Secondary

End point timeframe:

First dose of study drug to 30 days after last dose (Up to 18.9 months)

End point values	Alisertib 50 mg (Acute myeloid leukemia)	Alisertib 50 mg (Myelodysplastic syndrome)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	11		
Units: participants				
Febrile neutropenia	17	4		
Anaemia	14	3		
Thrombocytopenia	9	2		

Neutropenia	5	3		
Leukopenia	3	2		
Hypoalbuminaemia	4	0		
Leukocytosis	3	0		
Hypokalaemia	3	0		
Hyponatraemia	3	0		
Neutrophil count decreased	3	0		
Hypocalcaemia	2	0		
Clostridium difficile colitis	2	0		
Febrile bone marrow aplasia	1	0		
Hypoxia	1	0		
Hyperkalaemia	1	0		
Hypernatraemia	1	0		
Hyperglycaemia	1	0		
Hypoglycaemia	1	0		
Hypomagnesaemia	0	1		
Hypophospataemia	1	0		
Alanine aminotransferase increased	0	1		
Blood bilirubin increased	1	0		
Oxygen saturation decreased	1	0		
Blood culture positive	1	0		
Blood magnesium decreased	1	0		
Blood creatinine increased	1	0		
White blood cell count decreased	1	0		
Gilbert’s syndrome	1	0		
Lymphoedema	1	0		
Platelet count decreased	1	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First dose of study drug to 30 days after last dose (Up to 18.9 Months)

Adverse event reporting additional description:

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

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups

Reporting group title	Alisertib 50 mg (Acute myeloid leukemia)

Reporting group description:

Participants with acute myeloid leukemia received alisertib 50 mg, capsules, orally, twice daily for 7 days, followed by 14-day washout period, in 21-day cycles until disease progression or unacceptable treatment-related toxicity (Up to 26 Cycles).

Reporting group title	Alisertib 50 mg (Myelodysplastic syndrome)

Reporting group description:

Participants with myelodysplastic syndrome received alisertib 50 mg, capsules, orally, twice daily for 7 days, followed by 14-day washout period, in 21-day cycles until disease progression or unacceptable treatment-related toxicity (Up to 6 Cycles).

Serious adverse events	Alisertib 50 mg (Acute myeloid leukemia)	Alisertib 50 mg (Myelodysplastic syndrome)	
Total subjects affected by serious adverse events			
subjects affected / exposed	36 / 46 (78.26%)	8 / 11 (72.73%)	
number of deaths (all causes)	22	2	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia	Additional description: Five treatment-emergent deaths occurred in AML reporting group during treatment with alisertib 50 mg and were not related.		
subjects affected / exposed	5 / 46 (10.87%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 5	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 46 (2.17%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration			

site conditions			
Disease progression	Additional description: Four treatment-emergent deaths occurred in AML reporting group during treatment with alisertib 50 mg were not related and one treatment-emergent death occurred in MDS reporting group during treatment with alisertib 50 mg was not related.		
subjects affected / exposed	4 / 46 (8.70%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 4	0 / 1	
Fatigue			
subjects affected / exposed	1 / 46 (2.17%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 46 (2.17%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure	Additional description: One treatment-emergent death occurred in MDS reporting group during treatment with alisertib 50 mg and was not related.		
subjects affected / exposed	0 / 46 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Asthenia			
subjects affected / exposed	1 / 46 (2.17%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthermia			
subjects affected / exposed	1 / 46 (2.17%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 46 (2.17%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			

subjects affected / exposed	2 / 46 (4.35%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 46 (2.17%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 46 (2.17%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure	Additional description: One treatment-emergent death occurred in AML reporting group during treatment with alisertib 50 mg and was not related.		
subjects affected / exposed	1 / 46 (2.17%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Injury, poisoning and procedural complications			
Subdural haematoma	Additional description: One treatment-emergent death occurred in AML reporting group during treatment with alisertib 50 mg and was not related.		
subjects affected / exposed	1 / 46 (2.17%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 46 (2.17%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 46 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	0 / 46 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transfusion reaction			

subjects affected / exposed	1 / 46 (2.17%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 46 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 46 (2.17%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 46 (2.17%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 46 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral haemorrhage	Additional description: One treatment-emergent death occurred in AML reporting group during treatment with alisertib 50 mg and was not related.		
subjects affected / exposed	1 / 46 (2.17%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haemorrhage intracranial	Additional description: One treatment-emergent death occurred in AML reporting group during treatment with alisertib 50 mg and was not related.		
subjects affected / exposed	1 / 46 (2.17%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Depressed level of consciousness			
subjects affected / exposed	1 / 46 (2.17%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Somnolence			
subjects affected / exposed	1 / 46 (2.17%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 46 (2.17%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	13 / 46 (28.26%)	4 / 11 (36.36%)	
occurrences causally related to treatment / all	5 / 17	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	4 / 46 (8.70%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile bone marrow aplasia			
subjects affected / exposed	1 / 46 (2.17%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 46 (2.17%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness unilateral			
subjects affected / exposed	1 / 46 (2.17%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Stomatitis			

subjects affected / exposed	2 / 46 (4.35%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 46 (2.17%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 46 (2.17%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 46 (2.17%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 46 (2.17%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 46 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal inflammation			
subjects affected / exposed	0 / 46 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 46 (2.17%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			

subjects affected / exposed	1 / 46 (2.17%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth haemorrhage			
subjects affected / exposed	1 / 46 (2.17%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 46 (2.17%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure acute	Additional description: One treatment-emergent death occurred in AML reporting group during treatment with alisertib 50 mg and was not related.		
subjects affected / exposed	2 / 46 (4.35%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cystitis haemorrhagic			
subjects affected / exposed	1 / 46 (2.17%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 46 (2.17%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	1 / 46 (2.17%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck mass			
subjects affected / exposed	1 / 46 (2.17%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Sepsis	Additional description: Three treatment-emergent deaths occurred in AML reporting group during treatment with alisertib 50 mg and were not related.		
subjects affected / exposed	5 / 46 (10.87%)	2 / 11 (18.18%)	
occurrences causally related to treatment / all	1 / 8	0 / 2	
deaths causally related to treatment / all	0 / 3	0 / 0	
Pneumonia			
subjects affected / exposed	4 / 46 (8.70%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	1 / 46 (2.17%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection			
subjects affected / exposed	1 / 46 (2.17%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial sepsis	Additional description: One treatment-emergent death occurred in AML reporting group during treatment with alisertib 50 mg and was not related.		
subjects affected / exposed	1 / 46 (2.17%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Septic shock	Additional description: One treatment-emergent death occurred in AML reporting group during treatment with alisertib 50 mg and was not related.		
subjects affected / exposed	1 / 46 (2.17%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 46 (2.17%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection	Additional description: One treatment-emergent death occurred in AML reporting group during treatment with alisertib 50 mg and was not related.		
subjects affected / exposed	1 / 46 (2.17%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Vulvovaginal mycotic infection			
subjects affected / exposed	1 / 46 (2.17%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Serratia bacteraemia			
subjects affected / exposed	1 / 46 (2.17%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 46 (4.35%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Alisertib 50 mg (Acute myeloid leukemia)	Alisertib 50 mg (Myelodysplastic syndrome)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	45 / 46 (97.83%)	11 / 11 (100.00%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	7 / 46 (15.22%)	0 / 11 (0.00%)	
occurrences (all)	8	0	
Hypertension			
subjects affected / exposed	1 / 46 (2.17%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	15 / 46 (32.61%)	5 / 11 (45.45%)	
occurrences (all)	16	6	
Oedema peripheral			
subjects affected / exposed	12 / 46 (26.09%)	0 / 11 (0.00%)	
occurrences (all)	14	0	
Pyrexia			

subjects affected / exposed	9 / 46 (19.57%)	2 / 11 (18.18%)	
occurrences (all)	15	3	
Asthenia			
subjects affected / exposed	8 / 46 (17.39%)	1 / 11 (9.09%)	
occurrences (all)	8	1	
Chills			
subjects affected / exposed	6 / 46 (13.04%)	1 / 11 (9.09%)	
occurrences (all)	7	1	
Axillary pain			
subjects affected / exposed	0 / 46 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Catheter site erythema			
subjects affected / exposed	0 / 46 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Non-cardiac chest pain			
subjects affected / exposed	0 / 46 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	9 / 46 (19.57%)	3 / 11 (27.27%)	
occurrences (all)	10	3	
Epistaxis			
subjects affected / exposed	5 / 46 (10.87%)	3 / 11 (27.27%)	
occurrences (all)	6	3	
Oropharyngeal pain			
subjects affected / exposed	3 / 46 (6.52%)	3 / 11 (27.27%)	
occurrences (all)	4	3	
Pleural effusion			
subjects affected / exposed	4 / 46 (8.70%)	0 / 11 (0.00%)	
occurrences (all)	4	0	
Dyspnoea exertional			
subjects affected / exposed	2 / 46 (4.35%)	1 / 11 (9.09%)	
occurrences (all)	2	1	
Sneezing			

subjects affected / exposed	0 / 46 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Dyspnoea			
subjects affected / exposed	10 / 46 (21.74%)	2 / 11 (18.18%)	
occurrences (all)	10	2	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	4 / 46 (8.70%)	0 / 11 (0.00%)	
occurrences (all)	5	0	
Confusional state			
subjects affected / exposed	2 / 46 (4.35%)	1 / 11 (9.09%)	
occurrences (all)	2	1	
Mental status changes			
subjects affected / exposed	0 / 46 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Psychotic disorder			
subjects affected / exposed	0 / 46 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Investigations			
Neutrophil count decreased			
subjects affected / exposed	3 / 46 (6.52%)	0 / 11 (0.00%)	
occurrences (all)	5	0	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 46 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	2 / 46 (4.35%)	3 / 11 (27.27%)	
occurrences (all)	2	4	
Excoriation			
subjects affected / exposed	0 / 46 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	2	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	4 / 46 (8.70%)	0 / 11 (0.00%)	
occurrences (all)	4	0	

Tachycardia			
subjects affected / exposed	3 / 46 (6.52%)	0 / 11 (0.00%)	
occurrences (all)	3	0	
Bradycardia			
subjects affected / exposed	0 / 46 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Nervous system disorders			
Somnolence			
subjects affected / exposed	11 / 46 (23.91%)	2 / 11 (18.18%)	
occurrences (all)	11	2	
Headache			
subjects affected / exposed	5 / 46 (10.87%)	2 / 11 (18.18%)	
occurrences (all)	5	2	
Balance disorder			
subjects affected / exposed	0 / 46 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Burning sensation			
subjects affected / exposed	0 / 46 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	2	
Depressed level of consciousness			
subjects affected / exposed	0 / 46 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Subdural hygroma			
subjects affected / exposed	0 / 46 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Dizziness			
subjects affected / exposed	4 / 46 (8.70%)	2 / 11 (18.18%)	
occurrences (all)	5	2	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	10 / 46 (21.74%)	3 / 11 (27.27%)	
occurrences (all)	12	5	
Thrombocytopenia			
subjects affected / exposed	8 / 46 (17.39%)	2 / 11 (18.18%)	
occurrences (all)	9	4	
Neutropenia			

subjects affected / exposed	5 / 46 (10.87%)	3 / 11 (27.27%)	
occurrences (all)	6	5	
Febrile neutropenia			
subjects affected / exposed	6 / 46 (13.04%)	0 / 11 (0.00%)	
occurrences (all)	7	0	
Leukopenia			
subjects affected / exposed	3 / 46 (6.52%)	2 / 11 (18.18%)	
occurrences (all)	3	3	
Leukocytosis			
subjects affected / exposed	3 / 46 (6.52%)	0 / 11 (0.00%)	
occurrences (all)	5	0	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	3 / 46 (6.52%)	0 / 11 (0.00%)	
occurrences (all)	3	0	
Eye disorders			
Vision blurred			
subjects affected / exposed	1 / 46 (2.17%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	21 / 46 (45.65%)	2 / 11 (18.18%)	
occurrences (all)	29	4	
Nausea			
subjects affected / exposed	19 / 46 (41.30%)	3 / 11 (27.27%)	
occurrences (all)	24	3	
Stomatitis			
subjects affected / exposed	13 / 46 (28.26%)	4 / 11 (36.36%)	
occurrences (all)	15	5	
Vomiting			
subjects affected / exposed	8 / 46 (17.39%)	2 / 11 (18.18%)	
occurrences (all)	10	2	
Dysphagia			
subjects affected / exposed	6 / 46 (13.04%)	0 / 11 (0.00%)	
occurrences (all)	7	0	
Abdominal pain upper			

subjects affected / exposed	4 / 46 (8.70%)	0 / 11 (0.00%)	
occurrences (all)	4	0	
Constipation			
subjects affected / exposed	3 / 46 (6.52%)	1 / 11 (9.09%)	
occurrences (all)	3	1	
Gingival bleeding			
subjects affected / exposed	4 / 46 (8.70%)	0 / 11 (0.00%)	
occurrences (all)	5	0	
Oral pain			
subjects affected / exposed	4 / 46 (8.70%)	0 / 11 (0.00%)	
occurrences (all)	4	0	
Haemorrhoids			
subjects affected / exposed	2 / 46 (4.35%)	1 / 11 (9.09%)	
occurrences (all)	2	2	
Proctalgia			
subjects affected / exposed	2 / 46 (4.35%)	1 / 11 (9.09%)	
occurrences (all)	2	1	
Abdominal distension			
subjects affected / exposed	1 / 46 (2.17%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Dyspepsia			
subjects affected / exposed	1 / 46 (2.17%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Tongue ulceration			
subjects affected / exposed	1 / 46 (2.17%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Anal fissure			
subjects affected / exposed	0 / 46 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Oral disorder			
subjects affected / exposed	0 / 46 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Abdominal pain			
subjects affected / exposed	11 / 46 (23.91%)	2 / 11 (18.18%)	
occurrences (all)	12	2	
Hepatobiliary disorders			

Cholelithiasis			
subjects affected / exposed	0 / 46 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	7 / 46 (15.22%)	4 / 11 (36.36%)	
occurrences (all)	7	4	
Petechiae			
subjects affected / exposed	4 / 46 (8.70%)	0 / 11 (0.00%)	
occurrences (all)	4	0	
Pruritus			
subjects affected / exposed	2 / 46 (4.35%)	2 / 11 (18.18%)	
occurrences (all)	2	2	
Blood blister			
subjects affected / exposed	1 / 46 (2.17%)	2 / 11 (18.18%)	
occurrences (all)	1	2	
Ecchymosis			
subjects affected / exposed	3 / 46 (6.52%)	0 / 11 (0.00%)	
occurrences (all)	3	0	
Night sweats			
subjects affected / exposed	3 / 46 (6.52%)	0 / 11 (0.00%)	
occurrences (all)	3	0	
Rash			
subjects affected / exposed	2 / 46 (4.35%)	1 / 11 (9.09%)	
occurrences (all)	2	3	
Rash pruritic			
subjects affected / exposed	2 / 46 (4.35%)	1 / 11 (9.09%)	
occurrences (all)	4	1	
Urticaria			
subjects affected / exposed	3 / 46 (6.52%)	0 / 11 (0.00%)	
occurrences (all)	4	0	
Rash macular			
subjects affected / exposed	0 / 46 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	4	
Renal and urinary disorders			

Haematuria			
subjects affected / exposed	3 / 46 (6.52%)	0 / 11 (0.00%)	
occurrences (all)	3	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 46 (6.52%)	2 / 11 (18.18%)	
occurrences (all)	3	2	
Neck pain			
subjects affected / exposed	3 / 46 (6.52%)	0 / 11 (0.00%)	
occurrences (all)	3	0	
Pain in extremity			
subjects affected / exposed	3 / 46 (6.52%)	0 / 11 (0.00%)	
occurrences (all)	4	0	
Arthralgia			
subjects affected / exposed	1 / 46 (2.17%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Myalgia			
subjects affected / exposed	1 / 46 (2.17%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Gouty arthritis			
subjects affected / exposed	0 / 46 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Infections and infestations			
Oral herpes			
subjects affected / exposed	4 / 46 (8.70%)	1 / 11 (9.09%)	
occurrences (all)	4	1	
Cellulitis			
subjects affected / exposed	3 / 46 (6.52%)	1 / 11 (9.09%)	
occurrences (all)	5	1	
Pneumonia			
subjects affected / exposed	3 / 46 (6.52%)	0 / 11 (0.00%)	
occurrences (all)	3	0	
Bronchitis			
subjects affected / exposed	1 / 46 (2.17%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Anal abscess			

subjects affected / exposed	0 / 46 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Aspergillosis			
subjects affected / exposed	0 / 46 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	0 / 46 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Oral candidiasis			
subjects affected / exposed	0 / 46 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	8 / 46 (17.39%)	0 / 11 (0.00%)	
occurrences (all)	9	0	
Hypoalbuminaemia			
subjects affected / exposed	4 / 46 (8.70%)	0 / 11 (0.00%)	
occurrences (all)	4	0	
Hypokalaemia			
subjects affected / exposed	3 / 46 (6.52%)	0 / 11 (0.00%)	
occurrences (all)	4	0	
Hyponatraemia			
subjects affected / exposed	3 / 46 (6.52%)	0 / 11 (0.00%)	
occurrences (all)	4	0	
Dehydration			
subjects affected / exposed	1 / 46 (2.17%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Hypomagnesaemia			
subjects affected / exposed	0 / 46 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 January 2009	Amendment 1 -Clarify eligibility of patients with high-grade (eg, high-risk) MDS, relevant to IPSS categories and relevant to prior treatment, including demethylating agents which were approved for MDS. -Remove the requirement for follow-up bone marrow biopsies after the baseline biopsy and aspirate, since the Standard of Care among participating investigators did not require serial biopsies for follow-up of disease control. - Clarify that glucose and albumin should be obtained at screening, not baseline.
26 March 2009	Amendment 2 -Due to the nature of the disease under study in this protocol, the specific requirement for repeat testing of CBC with differential in the setting of ANC < 500/mm^3 or a platelet count < 25,000/mm^3 was removed. - clarification that additional laboratory safety testing could be done on existing blood volume, if required locally.
27 August 2009	Amendment 3 1.Update to definitions for disease response and progression -Clarify/update the response criteria for MDS patients based on recent literature. -Update the AML response criteria as per revised IWG AML criteria -Add a secondary endpoint for patients with MDS: Evaluation of Hematologic Improvement (HI) that generally aligns with IWG criteria in myelodysplasia 2.Modify the criteria for resuming treatment with alisertib after drug has been held due to an adverse event 3.Enrollment of a minimum number of patients with AML and MDS. To assure balance in clinical experience from this study, this amendment specified that a minimum of 8 patients were to be enrolled in each disease group (ie, 8 patients with AML and 8 patients with MDS) in the first stage of the protocol. 4. Reduce the frequency and clarify reasons for bone marrow testing.
27 October 2010	Amendment 4 To provide opportunity for continued treatment with study drug alisertib beyond 12 months for patients who tolerated alisertib and experienced objective response or disease control -To provide a reduced Schedule of Events for patients who had been on the study for more than 12 months and who were tolerating treatment with evidence of disease control -To add restrictions for concomitant medications that are known potent UGT/CYP inducers -To confirm that the interim analysis would not be conducted -To update the current clinical experience section -To update the current risk section -To clarify language around completion of treatment and withdrawal from study -To update product complaint language for consistency with Millennium's administrative requirements -To update and move contact information for the medical monitor to the study manual.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported