# 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<br>Units: Subjects | | | |
| <60 years | 4 | 2 | 6 |
| ≥60 years | 42 | 9 | 51 |
| Age Continuous<br>Units: years | | | |
| arithmetic mean | 71.9 | 69.5 | |
| standard deviation | ± 7.41 | ± 12.50 | - |
| Gender, Male/Female<br>Units: Subjects | | | |
| Female | 22 | 3 | 25 |
| Male | 24 | 8 | 32 |
| Race/Ethnicity, Customized<br>Units: Subjects | | | |
| Hispanic or Latino | 2 | 0 | 2 |
| Not Hispanic or Latino | 34 | 9 | 43 |
| Not Reported | 10 | 2 | 12 |
| Region of Enrollment<br>Units: Subjects | | | |
| United States | 33 | 9 | 42 |
| France | 11 | 2 | 13 |
| Canada | 2 | 0 | 2 |
| Race/Ethnicity, Customized<br>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<br>-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.<br>-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.<br>- Clarify that glucose and albumin should be obtained at screening, not baseline. |
| 26 March 2009 | Amendment 2<br>-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.<br>- clarification that additional laboratory safety testing could be done on existing blood volume, if required locally. |
| 27 August 2009 | Amendment 3<br>1.Update to definitions for disease response and progression<br>-Clarify/update the response criteria for MDS patients based on recent literature.<br>-Update the AML response criteria as per revised IWG AML criteria<br>-Add a secondary endpoint for patients with MDS: Evaluation of Hematologic Improvement (HI) that generally aligns with IWG criteria in myelodysplasia<br>2.Modify the criteria for resuming treatment with alisertib after drug has been held due to an adverse event<br>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.<br>4. Reduce the frequency and clarify reasons for bone marrow testing. |
| 27 October 2010 | Amendment 4<br>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<br>-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<br>-To add restrictions for concomitant medications that are known potent UGT/CYP inducers<br>-To confirm that the interim analysis would not be conducted<br>-To update the current clinical experience section<br>-To update the current risk section<br>-To clarify language around completion of treatment and withdrawal from study<br>-To update product complaint language for consistency with Millennium's administrative requirements<br>-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