# Clinical trial results:
# Open-Label, Multicenter Phase II Study For the Evaluation of Dasatinib (Sprycel™) Following Induction and Consolidation Therapy as well as in Maintenance Therapy in Patients With Newly Diagnosed Core-Binding Factor (CBF) Acute Myeloid Leukemia (AML)

## Summary

| | |
|---|---|
| EudraCT number | 2008-008238-35 |
| Trial protocol | DE AT |
| Global end of trial date | 30 November 2015 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 16 December 2016 |
| First version publication date | 16 December 2016 |
| Summary attachment (see zip file) | AMLSG 11-08 Final report (AMLSG11-08_finalreport_231116.pdf) |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | AMLSG11-08 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00850382 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Úniversitätsklinikum Ulm |
| Sponsor organisation address | Albert-Einstein-Allee 29, Ulm, Germany, 89081 |
| Public contact | AMLSG Studienzentrale, Universitätsklinikum Ulm, +49 731500 56072, |
| Scientific contact | Prof. Dr. Hartmut Döhner, Universitätsklinikum Ulm, +49 731500 45901, hartmut.doehner@uniklinik-ulm.de |

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 | 23 November 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 30 November 2015 |
| Global end of trial reached? | Yes |
| Global end of trial date | 30 November 2015 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

Primary Objective:
To assess the feasibility of dasatinib 100 mg QD given after intensive induction (daunorubicin and cytarabine) and consolidation chemotherapy (high-dose cytarabine) and as single agent in maintenance therapy.
The primary endpoint was a combined endpoint integrating the rates of early/hypoplastic death (Rate(ED/HD)), rate of pleural or pericardial effusion grade 3/4 (Rate(effuse)), rate of liver toxicity grade 3 or 4 that does not improve to grade 2 or less within 14 days after discontinuing responsible medication (Rate(liver)), and rate of refractory disease (Rate(RD)). Feasibility/tolerability for an individual patient was defined as a pleural or cardiac effusion level that does not exceed grade 2, as well as a liver toxicity equal to or less than grade 2 and the achievement of a complete remission after

Protection of trial subjects:

In this study, safety was assessed by evaluating the following: reported adverse events, clinical laboratory test results, vital signs measurements, ECG findings, chest X-ray, echo scan, physical examination findings, monitoring of concomitant therapy. For each safety parameter, all findings (whether normal or abnormal) were recorded in the CRF.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 25 June 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 | Austria: 8 |
| Country: Number of subjects enrolled | Germany: 83 |
| Worldwide total number of subjects | 91 |
| EEA total number of subjects | 91 |

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 | 0 |

| | |
|---|---|
| months) | |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 75 |
| From 65 to 84 years | 15 |
| 85 years and over | 1 |

## Subject disposition

### Recruitment

Recruitment details:

First patient in: 03.09.2009
Last patient last visit: 30.11.2015 (completion date)
After the enrollment of initially planned 25 patients on 22.06.2010, recruitment was interrupted until approval of the amended protocol Version 3.1 (01.09.2010). Re-cruitment was restarted on 01.12.2010. Overall, n=91 patients were enrolled

### Pre-assignment

Screening details:

Molecular genetic analysis (central AMLSG reference lab) of blood and bone marrow for CBF-associated gene fusions was performed at baseline within 48 hours to make an enrollment possible.

### Period 1

| | |
|---|---|
| Period 1 title | Enrollment |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

### Arms

| | |
|---|---|
| **Arm title** | Treatment |

Arm description:

All patients received induction chemotherapy (cytarabine and daunorubicin) in combination with dasatinib followed by consolidation therapy with either high-dose cytarabine in combination with dasatinib. After consolidation therapy a one-year maintenance therapy with dasatinib (continuously over 365 days) was intended in all patients.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Dasatinib |
| Investigational medicinal product code | |
| Other name | Sprycel |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Dasatinib was administered oral, in a daily dose of 100 mg (one a day, two tablets à 50
Patients should have taken their daily dose at approximately the same time in the morning. Each daily dose should have beene given with food and a glass of water (~240 mL). Patients should have been instructed to swallow capsules whole and not chew capsules.

Induction therapy:
100 mg/day, days 8-21
Consolidation therapy:
100 mg/day, days 6-28
Maintenance therapy:
100 mg/day over 365 days

| **Number of subjects in period 1** | Treatment |
|---|---|
| Started | 91 |
| Completed | 89 |
| Not completed | 2 |
| violation of inclusion/exclusion criteria | 2 |

## Period 2

| | |
|---|---|
| Period 2 title | Overall trial |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

## Arms

| | |
|---|---|
| **Arm title** | Treatment |

Arm description:

All patients received induction chemotherapy (cytarabine and daunorubicin) in combination with dasatinib followed by consolidation therapy with either high-dose cytarabine in combination with dasatinib. After consolidation therapy a one-year maintenance therapy with dasatinib (continuously over 365 days) was intended in all patients.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Dasatinib |
| Investigational medicinal product code | |
| Other name | Sprycel |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Dasatinib was administered oral, in a daily dose of 100 mg (one a day, two tablets à 50
Patients should have taken their daily dose at approximately the same time in the morning. Each daily dose should have beene given with food and a glass of water (~240 mL). Patients should have been instructed to swallow capsules whole and not chew capsules.

Induction therapy:
100 mg/day, days 8-21
Consolidation therapy:
100 mg/day, days 6-28
Maintenance therapy:
100 mg/day over 365 days

| **Number of subjects in period 2** | Treatment |
|---|---|
| Started | 89 |
| Induction cycle I | 89 |
| Induction cycle II (optional) | 7 [1] |
| Consolidation cycle I | 69 |
| Consolidation cycle II | 64 |
| Consolidation cycle III | 61 |
| Consolidation cycle IV | 55 |
| Maintenance therapy | 53 |
| Completed | 22 |
| Not completed | 67 |
| Adverse event, serious fatal | 4 |
| Consent withdrawn by subject | 5 |

| | |
|---|---|
| Adverse event, non-fatal | 33 |
| Other reasons | 2 |
| Lack of efficacy | 23 |

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Induction cycle II was administered only in patients not achieving a CR/CRi after Induction cycle I. Therefore, only 7 patients started this Milestone. 69 patients started consolidation cycle I, either directly after induction cycle I or after induction cycle II.

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Enrollment |

Reporting group description: -

| Reporting group values | Enrollment | Total | |
|---|---|---|---|
| Number of subjects | 91 | 91 | |
| Age categorical<br>Units: Subjects | | | |
| In utero | | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | | 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) | | 0 | |
| From 65-84 years | | 0 | |
| 85 years and over | | 0 | |
| Age continuous<br>Units: years | | | |
| median | 49.6 | | |
| full range (min-max) | 19 to 85 | - | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 43 | 43 | |
| Male | 48 | 48 | |
| ECOG Performance status<br>Units: Subjects | | | |
| Score 0 | 38 | 38 | |
| Score 1 | 40 | 40 | |
| Score 2 | 9 | 9 | |
| Not recorded | 4 | 4 | |
| Type of AML<br>Units: Subjects | | | |
| De Novo | 78 | 78 | |
| sAML | 2 | 2 | |
| tAML | 10 | 10 | |
| not recorded | 1 | 1 | |
| NPM1 mutation status<br>Units: Subjects | | | |
| Mutated | 0 | 0 | |
| Wildtype | 88 | 88 | |
| Not recorded | 3 | 3 | |
| FLT3 TKD status<br>Units: Subjects | | | |
| negative | 82 | 82 | |

| | | | |
|---|---|---|---|
| positive | 8 | 8 | |
| not recorded | 1 | 1 | |
| FLT3 ITD status<br>Units: Subjects | | | |
| positive | 4 | 4 | |
| negative | 86 | 86 | |
| not recorded | 1 | 1 | |
| KIT mutation status<br>Units: Subjects | | | |
| Mutation | 19 | 19 | |
| Wildtype | 66 | 66 | |
| not recorded | 6 | 6 | |
| NRAS mutation status<br>Units: Subjects | | | |
| Mutation | 27 | 27 | |
| Wildtype | 61 | 61 | |
| not recorded | 3 | 3 | |
| Type CBF<br>Units: Subjects | | | |
| t(8;21) | 37 | 37 | |
| inv(16) | 53 | 53 | |
| not recorded | 1 | 1 | |
| Hemoglobin<br>Units: g/dl | | | |
| median | 9.2 | | |
| full range (min-max) | 4.6 to 14.8 | - | |
| Platelets<br>Units: G/l | | | |
| median | 37 | | |
| full range (min-max) | 2 to 279 | - | |
| White blood count<br>Units: G/l | | | |
| median | 19.4 | | |
| full range (min-max) | 1.2 to 192.2 | - | |
| Bone marrow blasts<br>Units: per cent | | | |
| median | 70 | | |
| full range (min-max) | 11 to 95 | - | |
| Peripheral blood blasts<br>Units: per cent | | | |
| median | 38 | | |
| full range (min-max) | 0 to 94 | - | |

## Subject analysis sets

| | |
|---|---|
| Subject analysis set title | Full analysis set |
| Subject analysis set type | Full analysis |

Subject analysis set description:

All patients scheduled for study Treatment and started with induction cycle I were included into the full Analysis set which is used for efficacy and safety Analysis.

| **Reporting group values** | Full analysis set | | |
|---|---|---|---|
| Number of subjects | 89 | | |
| Age categorical<br>Units: Subjects | | | |
| In utero | | | |
| Preterm newborn infants (gestational age < 37 wks) | | | |
| Newborns (0-27 days) | | | |
| Infants and toddlers (28 days-23 months) | | | |
| Children (2-11 years) | | | |
| Adolescents (12-17 years) | | | |
| Adults (18-64 years) | | | |
| From 65-84 years | | | |
| 85 years and over | | | |
| Age continuous<br>Units: years | | | |
| median | 49.5 | | |
| full range (min-max) | 19 to 73 | | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 42 | | |
| Male | 47 | | |
| ECOG Performance status<br>Units: Subjects | | | |
| Score 0 | 38 | | |
| Score 1 | 39 | | |
| Score 2 | 9 | | |
| Not recorded | 3 | | |
| Type of AML<br>Units: Subjects | | | |
| De Novo | 77 | | |
| sAML | 2 | | |
| tAML | 10 | | |
| not recorded | 0 | | |
| NPM1 mutation status<br>Units: Subjects | | | |
| Mutated | 0 | | |
| Wildtype | 86 | | |
| Not recorded | 3 | | |
| FLT3 TKD status<br>Units: Subjects | | | |
| negative | 81 | | |
| positive | 7 | | |
| not recorded | 1 | | |
| FLT3 ITD status<br>Units: Subjects | | | |
| positive | 4 | | |
| negative | 84 | | |
| not recorded | 1 | | |
| KIT mutation status<br>Units: Subjects | | | |

| | | | |
|---|---|---|---|
| Mutation | 19 | | |
| Wildtype | 65 | | |
| not recorded | 5 | | |
| NRAS mutation status<br>Units: Subjects | | | |
| Mutation | 27 | | |
| Wildtype | 60 | | |
| not recorded | 2 | | |
| Type CBF<br>Units: Subjects | | | |
| t(8;21) | 37 | | |
| inv(16) | 52 | | |
| not recorded | 0 | | |
| Hemoglobin<br>Units: g/dl | | | |
| median | 9.2 | | |
| full range (min-max) | 4.6 to 14.8 | | |
| Platelets<br>Units: G/l | | | |
| median | 37 | | |
| full range (min-max) | 2 to 279 | | |
| White blood count<br>Units: G/l | | | |
| median | 19.4 | | |
| full range (min-max) | 1.2 to 192.2 | | |
| Bone marrow blasts<br>Units: per cent | | | |
| median | 70 | | |
| full range (min-max) | 11 to 95 | | |
| Peripheral blood blasts<br>Units: per cent | | | |
| median | 40 | | |
| full range (min-max) | 0 to 94 | | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Treatment |

Reporting group description:

All patients received induction chemotherapy (cytarabine and daunorubicin) in combination with dasatinib followed by consolidation therapy with either high-dose cytarabine in combination with dasatinib. After consolidation therapy a one-year maintenance therapy with dasatinib (continuously over 365 days) was intended in all patients.

| | |
|---|---|
| Reporting group title | Treatment |

Reporting group description:

All patients received induction chemotherapy (cytarabine and daunorubicin) in combination with dasatinib followed by consolidation therapy with either high-dose cytarabine in combination with dasatinib. After consolidation therapy a one-year maintenance therapy with dasatinib (continuously over 365 days) was intended in all patients.

| | |
|---|---|
| Subject analysis set title | Full analysis set |
| Subject analysis set type | Full analysis |

Subject analysis set description:

All patients scheduled for study Treatment and started with induction cycle I were included into the full Analysis set which is used for efficacy and safety Analysis.

### Primary: Feasibility

| | |
|---|---|
| End point title | Feasibility[1] |

End point description:

The primary endpoint was a combined endpoint integrating the rates of early/hypoplastic death (Rate(ED/HD)), rate of pleural or pericardial effusion grade 3/4 (Rate(effuse)), rate of liver toxicity grade 3 or 4 that does not improve to grade 2 or less within 14 days after discontinuing responsible medication (Rate(liver)), and rate of refractory disease (Rate(RD)). Feasibility/tolerability for an individual patient was defined as a pleural or cardiac effusion level that does not exceed grade 2, as well as a liver toxicity equal to or less than grade 2 and the achievement of a complete remission after

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

End point timeframe:

Whole Treatment period of patients (maximally 19 months)

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 analysis was done for Primary endpoint. Everytime an event of one of the four single endpoints occured, the cumulative number of Events of the specific endpoint was compared to the predefined critial number of Events at this enrollment stage (current number of enrolled patients). At every sequential testing time point during the study and for all single primary endpoints, the cum. number of events was below the critical value. Thus, primary endpoint was met, feasibility was shown.

| End point values | Treatment | Full analysis set | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 89 | 89 | | |
| Units: subject | | | | |
| Refractory Disease | 2 | 2 | | |
| Early Death/Hypoplastic Death | 4 | 4 | | |
| Pleural/pericardial effusion | 6 | 6 | | |
| Liver toxicities | 6 | 6 | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Overall survival

| End point title | Overall survival |
|---|---|

End point description:

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

End point timeframe:

4 years after inclusion into the study

| End point values | Treatment | Full analysis set | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 89 | 89 | | |
| Units: per cent | | | | |
| number (confidence interval 95%) | 74.7 (66.1 to 84.5) | 74.7 (66.1 to 84.5) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Cumulative incidence of relapse

| End point title | Cumulative incidence of relapse |
|---|---|

End point description:

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

End point timeframe:

4 years after inclusion into the trial

| End point values | Treatment | Full analysis set | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 73 | 73 | | |
| Units: per cent | | | | |
| number (not applicable) | 35.2 | 35.2 | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Cumulative incidence of death

| End point title | Cumulative incidence of death |
|---|---|

End point description:

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

End point timeframe:

after 4 years after inclusion into the trial

| End point values | Treatment | Full analysis set | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 73 | 73 | | |
| Units: per cent | | | | |
| number (not applicable) | 4.2 | 4.2 | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

The adverse event reporting period for this trial began upon signing of informed consent and ended 28 days after the last treatment administration or until all drug-related toxicities were resolved, whichever was later or until the Investigators assessed

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

### Dictionary used

| | |
|---|---|
| Dictionary name | CTCAE |
| Dictionary version | 3.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Safety data set |

Reporting group description:

The safety analysis set included 89 patients scheduled for study Treatment.

| Serious adverse events | Safety data set | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 56 / 89 (62.92%) | | |
| number of deaths (all causes) | 5 | | |
| number of deaths resulting from adverse events | 3 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Secondary malingancy (possibly related to cancer treatment) | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Thrombosis/embolism | | | |
| subjects affected / exposed | 2 / 89 (2.25%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Other vascular disorder | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Fever | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 3 / 89 (3.37%) | | | |
| occurrences causally related to treatment / all | 4 / 7 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Rigor/chills | | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Death not associated with CTCAE term | | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Other haemorrhage | | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Other disorders | | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Reproductive system and breast disorders | | | | |
| Other pulmonary disorder | | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Respiratory, thoracic and mediastinal disorders | | | | |
| Airway obstruction | | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 1 / 1 | | | |
| Dyspnea | | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 1 / 89 (1.12%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pleural effusion | | | | |
| subjects affected / exposed | 4 / 89 (4.49%) | | | |
| occurrences causally related to treatment / all | 4 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonitis | | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Investigations | | | | |
| CRP increase | | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cardiac disorders | | | | |
| Supraventricular arrhythmia | | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Other cardiac disorders | | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cardiac ischemia/infarction | | | | |
| subjects affected / exposed | 2 / 89 (2.25%) | | | |
| occurrences causally related to treatment / all | 1 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| cTnT | | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hypotension | | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 1 / 89 (1.12%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Left ventricular systolic dysfunction | | | | |
| subjects affected / exposed | 2 / 89 (2.25%) | | | |
| occurrences causally related to treatment / all | 2 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Nervous system disorders | | | | |
| CNS hemorrhage | | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Dizziness | | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Neuropathy sensory | | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Psychosis | | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Seizure | | | | |
| subjects affected / exposed | 2 / 89 (2.25%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Somnolence | | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Blood and lymphatic system disorders | | | | |

| | | | |
|---|---|---|---|
| Blood - Other disorders | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hemoglobin | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Leukocytes | | | |
| subjects affected / exposed | 2 / 89 (2.25%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neutrophils | | | |
| subjects affected / exposed | 2 / 89 (2.25%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Platelets | | | |
| subjects affected / exposed | 4 / 89 (4.49%) | | |
| occurrences causally related to treatment / all | 3 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Splenic function | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ear and labyrinth disorders | | | |
| Blurred vision | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Ascites | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|---|---|---|
| Colitis | | | |
| subjects affected / exposed | 3 / 89 (3.37%) | | |
| occurrences causally related to treatment / all | 6 / 7 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Constipation | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diarrhea | | | |
| subjects affected / exposed | 2 / 89 (2.25%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Enteritis | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Other gastrointestinal disorders | | | |
| subjects affected / exposed | 2 / 89 (2.25%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nausea | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hemorrhage gastrointestinal | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pain abdomen | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |

| | | | |
|---|---|---|---|
| Cholecystitis | | | |
| subjects affected / exposed | 3 / 89 (3.37%) | | |
| occurrences causally related to treatment / all | 1 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Other hepatobiliary disorders | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Petechiae | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Other renal disorder | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal failure | | | |
| subjects affected / exposed | 3 / 89 (3.37%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Trismus | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Colitis, infectious | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 5 / 89 (5.62%) | | | |
| occurrences causally related to treatment / all | 2 / 6 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Febrile neutropenia | | | | |
| subjects affected / exposed | 10 / 89 (11.24%) | | | |
| occurrences causally related to treatment / all | 6 / 13 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Sepsis | | | | |
| subjects affected / exposed | 18 / 89 (20.22%) | | | |
| occurrences causally related to treatment / all | 11 / 20 | | | |
| deaths causally related to treatment / all | 1 / 2 | | | |
| Other infection | | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infection abdomen | | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | | | |
| occurrences causally related to treatment / all | 2 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infection anal/perianal | | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infection colon | | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | | | |
| occurrences causally related to treatment / all | 1 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infection peritoneal cavity | | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lung (pneumonia) | | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 17 / 89 (19.10%) | | |
| occurrences causally related to treatment / all | 9 / 18 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infection pleura (empyema) | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infection upper airway | | | |
| subjects affected / exposed | 2 / 89 (2.25%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infection urinary tract | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | | |
| occurrences causally related to treatment / all | 2 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| **Non-serious adverse events** | Safety data set | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 89 / 89 (100.00%) | | |
| Vascular disorders | | | |
| Phlebitis | | | |
| subjects affected / exposed | 8 / 89 (8.99%) | | |
| occurrences (all) | 10 | | |
| Thrombosis/Embolism | | | |
| subjects affected / exposed | 6 / 89 (6.74%) | | |
| occurrences (all) | 6 | | |
| General disorders and administration site conditions | | | |
| Other constitutional symptom | | | |
| subjects affected / exposed | 7 / 89 (7.87%) | | |
| occurrences (all) | 11 | | |
| Fatigue | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 34 / 89 (38.20%) | | |
| occurrences (all) | 108 | | |
| Fever | | | |
| subjects affected / exposed | 58 / 89 (65.17%) | | |
| occurrences (all) | 183 | | |
| Insomnia | | | |
| subjects affected / exposed | 35 / 89 (39.33%) | | |
| occurrences (all) | 83 | | |
| rigor/chills | | | |
| subjects affected / exposed | 12 / 89 (13.48%) | | |
| occurrences (all) | 19 | | |
| sweating | | | |
| subjects affected / exposed | 7 / 89 (7.87%) | | |
| occurrences (all) | 9 | | |
| Weight gain | | | |
| subjects affected / exposed | 16 / 89 (17.98%) | | |
| occurrences (all) | 24 | | |
| Hemorrhage - other | | | |
| subjects affected / exposed | 10 / 89 (11.24%) | | |
| occurrences (all) | 14 | | |
| Pain - other | | | |
| subjects affected / exposed | 20 / 89 (22.47%) | | |
| occurrences (all) | 46 | | |
| Immune system disorders | | | |
| Allergic reaction | | | |
| subjects affected / exposed | 25 / 89 (28.09%) | | |
| occurrences (all) | 34 | | |
| Reproductive system and breast disorders | | | |
| Hemorrhage genitourinary | | | |
| subjects affected / exposed | 8 / 89 (8.99%) | | |
| occurrences (all) | 10 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Hemorrhage pulmonary | | | |
| subjects affected / exposed | 18 / 89 (20.22%) | | |
| occurrences (all) | 26 | | |
| Pain - Chest/thorax | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 11 / 89 (12.36%) | | |
| occurrences (all) | 17 | | |
| Pain - Throat/pharynx/larynx | | | |
| subjects affected / exposed | 10 / 89 (11.24%) | | |
| occurrences (all) | 11 | | |
| Cough | | | |
| subjects affected / exposed | 25 / 89 (28.09%) | | |
| occurrences (all) | 39 | | |
| Dyspnea | | | |
| subjects affected / exposed | 19 / 89 (21.35%) | | |
| occurrences (all) | 32 | | |
| Pleural effusion | | | |
| subjects affected / exposed | 16 / 89 (17.98%) | | |
| occurrences (all) | 46 | | |
| Pneumonitis | | | |
| subjects affected / exposed | 10 / 89 (11.24%) | | |
| occurrences (all) | 13 | | |
| Investigations | | | |
| Alanine aminotransferase | | | |
| subjects affected / exposed | 17 / 89 (19.10%) | | |
| occurrences (all) | 44 | | |
| Aspartate aminotransferase | | | |
| subjects affected / exposed | 15 / 89 (16.85%) | | |
| occurrences (all) | 33 | | |
| Bilirubin | | | |
| subjects affected / exposed | 7 / 89 (7.87%) | | |
| occurrences (all) | 12 | | |
| Gamma-glutamyltransferase | | | |
| subjects affected / exposed | 10 / 89 (11.24%) | | |
| occurrences (all) | 17 | | |
| Hyperuricemia | | | |
| subjects affected / exposed | 5 / 89 (5.62%) | | |
| occurrences (all) | 6 | | |
| Hypoalbuminemia | | | |
| subjects affected / exposed | 5 / 89 (5.62%) | | |
| occurrences (all) | 6 | | |

| | | | |
|---|---|---|---|
| Hypocalcemia<br>subjects affected / exposed<br>occurrences (all) | 14 / 89 (15.73%)<br>34 | | |
| Hypokalemia<br>subjects affected / exposed<br>occurrences (all) | 40 / 89 (44.94%)<br>129 | | |
| Hypomagnesemia<br>subjects affected / exposed<br>occurrences (all) | 10 / 89 (11.24%)<br>23 | | |
| CRP increase<br>subjects affected / exposed<br>occurrences (all) | 17 / 89 (19.10%)<br>61 | | |
| Other lab disorders<br>subjects affected / exposed<br>occurrences (all) | 18 / 89 (20.22%)<br>36 | | |
| Cardiac disorders<br>Cardiac arrhythmia - other<br>subjects affected / exposed<br>occurrences (all) | 5 / 89 (5.62%)<br>14 | | |
| Supraventricular arrhythmia<br>subjects affected / exposed<br>occurrences (all) | 9 / 89 (10.11%)<br>19 | | |
| Hypertension<br>subjects affected / exposed<br>occurrences (all) | 17 / 89 (19.10%)<br>47 | | |
| Hypotension<br>subjects affected / exposed<br>occurrences (all) | 14 / 89 (15.73%)<br>23 | | |
| Pericardial effusion<br>subjects affected / exposed<br>occurrences (all) | 6 / 89 (6.74%)<br>10 | | |
| Nervous system disorders<br>Dizziness<br>subjects affected / exposed<br>occurrences (all) | 20 / 89 (22.47%)<br>43 | | |
| Mood alteration - agitation | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 5 / 89 (5.62%) | | |
| occurrences (all) | 8 | | |
| Mood alteration - anxiety | | | |
| subjects affected / exposed | 11 / 89 (12.36%) | | |
| occurrences (all) | 20 | | |
| Mood alteration - depression | | | |
| subjects affected / exposed | 12 / 89 (13.48%) | | |
| occurrences (all) | 24 | | |
| Neuropathy sensory | | | |
| subjects affected / exposed | 9 / 89 (10.11%) | | |
| occurrences (all) | 16 | | |
| Pain head/Headache | | | |
| subjects affected / exposed | 39 / 89 (43.82%) | | |
| occurrences (all) | 105 | | |
| Blood and lymphatic system disorders | | | |
| Hemoglobin | | | |
| subjects affected / exposed | 72 / 89 (80.90%) | | |
| occurrences (all) | 358 | | |
| Leukocytes | | | |
| subjects affected / exposed | 53 / 89 (59.55%) | | |
| occurrences (all) | 238 | | |
| Neutrophils | | | |
| subjects affected / exposed | 27 / 89 (30.34%) | | |
| occurrences (all) | 79 | | |
| Platelets | | | |
| subjects affected / exposed | 72 / 89 (80.90%) | | |
| occurrences (all) | 364 | | |
| Edema head and neck | | | |
| subjects affected / exposed | 8 / 89 (8.99%) | | |
| occurrences (all) | 25 | | |
| Edema limb | | | |
| subjects affected / exposed | 10 / 89 (11.24%) | | |
| occurrences (all) | 17 | | |
| Eye disorders | | | |
| Dry eye | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 13 / 89 (14.61%) | | |
| occurrences (all) | 25 | | |
| Other ocular disorder | | | |
| subjects affected / exposed | 10 / 89 (11.24%) | | |
| occurrences (all) | 13 | | |
| Gastrointestinal disorders | | | |
| Anorexia | | | |
| subjects affected / exposed | 16 / 89 (17.98%) | | |
| occurrences (all) | 30 | | |
| Colitis | | | |
| subjects affected / exposed | 7 / 89 (7.87%) | | |
| occurrences (all) | 10 | | |
| Constipation | | | |
| subjects affected / exposed | 39 / 89 (43.82%) | | |
| occurrences (all) | 100 | | |
| Diarrhea | | | |
| subjects affected / exposed | 61 / 89 (68.54%) | | |
| occurrences (all) | 162 | | |
| Enteritis | | | |
| subjects affected / exposed | 5 / 89 (5.62%) | | |
| occurrences (all) | 9 | | |
| Flatulence | | | |
| subjects affected / exposed | 11 / 89 (12.36%) | | |
| occurrences (all) | 28 | | |
| Gastritis | | | |
| subjects affected / exposed | 5 / 89 (5.62%) | | |
| occurrences (all) | 5 | | |
| Other gastrointestinal disorder | | | |
| subjects affected / exposed | 13 / 89 (14.61%) | | |
| occurrences (all) | 19 | | |
| Heartburn | | | |
| subjects affected / exposed | 9 / 89 (10.11%) | | |
| occurrences (all) | 19 | | |
| Mucositis | | | |
| subjects affected / exposed | 37 / 89 (41.57%) | | |
| occurrences (all) | 49 | | |

| | | | |
|---|---|---|---|
| Nausea | | | |
| subjects affected / exposed | 74 / 89 (83.15%) | | |
| occurrences (all) | 248 | | |
| Taste alteration | | | |
| subjects affected / exposed | 9 / 89 (10.11%) | | |
| occurrences (all) | 15 | | |
| Vomiting | | | |
| subjects affected / exposed | 45 / 89 (50.56%) | | |
| occurrences (all) | 106 | | |
| Hemorrhage gastrointestinal | | | |
| subjects affected / exposed | 6 / 89 (6.74%) | | |
| occurrences (all) | 7 | | |
| Pain - abdomen | | | |
| subjects affected / exposed | 29 / 89 (32.58%) | | |
| occurrences (all) | 77 | | |
| Pain - anus | | | |
| subjects affected / exposed | 7 / 89 (7.87%) | | |
| occurrences (all) | 9 | | |
| Pain - Dental / teeth | | | |
| subjects affected / exposed | 8 / 89 (8.99%) | | |
| occurrences (all) | 10 | | |
| Pain - Stomach | | | |
| subjects affected / exposed | 19 / 89 (21.35%) | | |
| occurrences (all) | 35 | | |
| Skin and subcutaneous tissue disorders | | | |
| Dermatology - other disorder | | | |
| subjects affected / exposed | 10 / 89 (11.24%) | | |
| occurrences (all) | 14 | | |
| Dry skin | | | |
| subjects affected / exposed | 5 / 89 (5.62%) | | |
| occurrences (all) | 5 | | |
| Hand - foot syndrom | | | |
| subjects affected / exposed | 5 / 89 (5.62%) | | |
| occurrences (all) | 6 | | |
| Injection site reaction | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 13 / 89 (14.61%) | | |
| occurrences (all) | 21 | | |
| Pruritus | | | |
| subjects affected / exposed | 16 / 89 (17.98%) | | |
| occurrences (all) | 18 | | |
| Rash | | | |
| subjects affected / exposed | 53 / 89 (59.55%) | | |
| occurrences (all) | 113 | | |
| Hematoma | | | |
| subjects affected / exposed | 10 / 89 (11.24%) | | |
| occurrences (all) | 12 | | |
| Petechiae | | | |
| subjects affected / exposed | 16 / 89 (17.98%) | | |
| occurrences (all) | 27 | | |
| Renal and urinary disorders | | | |
| Fluid retention | | | |
| subjects affected / exposed | 36 / 89 (40.45%) | | |
| occurrences (all) | 95 | | |
| Other renal disorders | | | |
| subjects affected / exposed | 7 / 89 (7.87%) | | |
| occurrences (all) | 9 | | |
| Renal failure | | | |
| subjects affected / exposed | 7 / 89 (7.87%) | | |
| occurrences (all) | 8 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Other musculoskeletal disorders | | | |
| subjects affected / exposed | 5 / 89 (5.62%) | | |
| occurrences (all) | 5 | | |
| Pain - Back | | | |
| subjects affected / exposed | 28 / 89 (31.46%) | | |
| occurrences (all) | 56 | | |
| Pain - Bone | | | |
| subjects affected / exposed | 10 / 89 (11.24%) | | |
| occurrences (all) | 16 | | |
| Pain - Extremity | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 9 / 89 (10.11%) | | |
| occurrences (all) | 12 | | |
| Pain - Joint | | | |
| subjects affected / exposed | 23 / 89 (25.84%) | | |
| occurrences (all) | 39 | | |
| Pain - Neck | | | |
| subjects affected / exposed | 6 / 89 (6.74%) | | |
| occurrences (all) | 9 | | |
| Infections and infestations | | | |
| Colitis, Infectious | | | |
| subjects affected / exposed | 6 / 89 (6.74%) | | |
| occurrences (all) | 7 | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 39 / 89 (43.82%) | | |
| occurrences (all) | 81 | | |
| Sepsis | | | |
| subjects affected / exposed | 24 / 89 (26.97%) | | |
| occurrences (all) | 56 | | |
| Other infection | | | |
| subjects affected / exposed | 43 / 89 (48.31%) | | |
| occurrences (all) | 96 | | |
| Lip/perioral infection | | | |
| subjects affected / exposed | 14 / 89 (15.73%) | | |
| occurrences (all) | 23 | | |
| Infection anal/perianal | | | |
| subjects affected / exposed | 6 / 89 (6.74%) | | |
| occurrences (all) | 8 | | |
| Infection oral cavity/gums (gingivitis) | | | |
| subjects affected / exposed | 8 / 89 (8.99%) | | |
| occurrences (all) | 8 | | |
| Infection catheter-related | | | |
| subjects affected / exposed | 12 / 89 (13.48%) | | |
| occurrences (all) | 26 | | |
| Lung (pneumonia) | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 31 / 89 (34.83%) | | |
| occurrences (all) | 53 | | |
| Infection upper airways | | | |
| subjects affected / exposed | 22 / 89 (24.72%) | | |
| occurrences (all) | 40 | | |
| Infection urinary tract | | | |
| subjects affected / exposed | 13 / 89 (14.61%) | | |
| occurrences (all) | 33 | | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 17 August 2009 | Amendment 1 (dated 17 August 2009) was issued before start of patient enrollment. There were no changes made to the protocol, but new investigational sites and investigators introduced to the study. |
| 04 February 2010 | Amendment 2 (dated 04 February 2010) to the protocol was issued after 11 patients were enrolled into the study. The major changes made to the protocol were due to integration of Austria as new country with four new investigational sites. |
| 01 September 2010 | Amendment 3 (dated 01 September 2010) to the protocol was issued after 25 patients were enrolled and intial planned study cohort was completed.<br>The following major procedural changes (not all-inclusive) were made to the protocol:<br>• Increase of sample size to additional 57 patients (overall sample size = 82 patients).<br>• Implementation of an optional second induction cycle for patients not achieving complete remission after the first induction cycle. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|---|---|---|
| 22 June 2010 | After the enrollment of initially planned 25 patients on 22.06.2010, recruitment was interrupted until approval of the amended protocol Version 3.1 (01.09.2010). Re-cruitment was restarted on 01.12.2010. | 01 December 2010 |

Notes:

### Limitations and caveats

None reported