# Clinical trial results:
# A Phase I/II study of clofarabine in combination with cytarabine and liposomal daunorubicin in children with relapsed/refractory pediatric AML

## Summary

| | |
|---|---|
| EudraCT number | 2009-009457-13 |
| Trial protocol | NL CZ AT FR DE |
| Global end of trial date | 02 April 2015 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 23 September 2020 |
| First version publication date | 23 September 2020 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | StudyITCC020&I-BFMRelapsedAML |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Nederlands Trial Register: NTR1880 |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Erasmus MC |
| Sponsor organisation address | Dr. Molenwaterplein 60, Rotterdam, Netherlands, 3015 GD |
| Public contact | Michel Zwaan, Erasmus MC, 31 107036691, c.m.zwaan@erasmusmc.nl |
| Scientific contact | Michel Zwaan, Erasmus MC, 31 107036691, c.m.zwaan@erasmusmc.nl |

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 | 12 June 2015 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 02 April 2015 |
| Global end of trial reached? | Yes |
| Global end of trial date | 02 April 2015 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To establish the recommended dose of clofarabine in combination with cytarabine and liposomal daunorubicin (DaunoXome®) in children with relapsed/refractory AML.

Note: dosages of cytarabine and liposomal daunorubicin should be comparable to those used in the current Relapsed AML 2001/01 study (i.e. in the context of the FLAG/liposomal daunorubicin regimen).

Protection of trial subjects:

By the informed consent and voluntary participation in the trial.
Surgical interventions take place under anaestesia.

Background therapy:

Cytarabine and liposomal daunorubicin

Evidence for comparator:

In this study the cytarabine dose as administered in the FLAG regimen (2 gram/m2 bolus IV for 5 consecutive days) is used – which will allow a fair comparison with the FLAG regimen in later studies.

| | |
|---|---|
| Actual start date of recruitment | 10 May 2010 |
| 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 | Netherlands: 13 |
| Country: Number of subjects enrolled | Austria: 4 |
| Country: Number of subjects enrolled | Czech Republic: 2 |
| Country: Number of subjects enrolled | France: 3 |
| Country: Number of subjects enrolled | Germany: 12 |
| Worldwide total number of subjects | 34 |
| EEA total number of subjects | 34 |

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) | 6 |
| Children (2-11 years) | 16 |
| Adolescents (12-17 years) | 10 |
| Adults (18-64 years) | 2 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Study initiation date/first subject first visit: May 10, 2010
Study completion date/last subject last visit: April 2, 2015
34 subjects enrolled.

### Pre-assignment

Screening details:

Patient eligibility:
- <19 years of age with early 1st relapse (within 12 months from initial diagnosis)
- refractory 1st relapse (≥20% blasts in the bone marrow after the 1st course of standard re-induction therapy)
- with at least a 2nd relapsed AML
Only patients with early 1st relapse without prior SCT were eligible for DL5.

### Period 1

| | |
|---|---|
| Period 1 title | overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Dose level 1 |

Arm description:

Clofarabine = 20 mg/m2/day x 5d, DaunoXome = 40 mg/m2/ d 1-3-5, Ara-C = 2 gr/m2/day x 5d

| | |
|---|---|
| Arm type | Dose level 1 |
| Investigational medicinal product name | Clofarabine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate and solvent for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

20 mg/m2/day x 5 days

| | |
|---|---|
| Investigational medicinal product name | Daunoxome |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate and solvent for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

40 mg/m2/day; day 1-3-5

| | |
|---|---|
| Investigational medicinal product name | Cytarabine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate and solvent for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

2 gr/m2/d x 5d

| | |
|---|---|
| **Arm title** | Dose level 2 |

Arm description:

Clofarabine = 30 mg/m2/day x 5d, DaunoXome = 40 mg/m2/ d 1-3-5, Ara-C = 2 gr/m2/day x 5d

| | |
|---|---|
| Arm type | Dose level 2 |
| Investigational medicinal product name | Clofarabine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate and solvent for solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details:<br>30 mg/m2/d x 5d | |
| Investigational medicinal product name | DaunoXome |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate and solvent for solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details:<br>40 mg/m2/d 1-3-5 | |
| Investigational medicinal product name | Cytarabine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate and solvent for solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details:<br>2 gr/m2/d x 5d | |
| **Arm title** | Dose level 3a |
| Arm description:<br>clofarabine = 30 mg/m2/day x 5d, DaunoXome = 60 mg/m2/ d 1-3-5, Ara-C = 2 gr/m2/day x 5d | |
| Arm type | Dose level 3a |
| Investigational medicinal product name | Clofarabine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate and solvent for solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details:<br>30 mg/m2/d x 5 d | |
| Investigational medicinal product name | DaunoXome |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate and solvent for solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details:<br>60 mg/m2/d 1-3-5 | |
| Investigational medicinal product name | Cytarabine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate and solvent for solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details:<br>2 gr/m2/d x 5 d | |
| **Arm title** | Dose level 3b |
| Arm description:<br>clofarabine = 30 mg/m2/day x 5d, DaunoXome = 60 mg/m2/ d 1-3-5, Ara-C = 2 gr/m2/day x 5d | |
| Arm type | Dose level 3b |

| | |
|---|---|
| Investigational medicinal product name | Clofarabine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate and solvent for solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details:<br>30 mg/m2/d x 5 d | |
| Investigational medicinal product name | DaunoXome |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate and solvent for solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details:<br>60 mg/m2/d 1-3-5 | |
| Investigational medicinal product name | Cytarabine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate and solvent for solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details:<br>2 gr/m2/d x 5 d | |
| **Arm title** | Dose level 4 |
| Arm description:<br>clofarabine = 40 mg/m2/day x 5d, DaunoXome = 60 mg/m2/ d 1-3-5, Ara-C = 2 gr/m2/day x 5d | |
| Arm type | Dose level 4 |
| Investigational medicinal product name | Clofarabine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate and solvent for solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details:<br>40 mg/m2/d x 5 d | |
| Investigational medicinal product name | DaunoXome |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate and solvent for solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details:<br>60 mg/m2/d 1-3-5 | |
| Investigational medicinal product name | Cytarabine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate and solvent for solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details:<br>2 gr/m2/d x 5 d | |
| **Arm title** | Dose level 5 |
| Arm description:<br>clofarabine = 40 mg/m2/day x 5d, DaunoXome = 80 mg/m2/ d 1-3-5, Ara-C = 2 gr/m2/day x 5d | |
| Arm type | Dose level 5 |

| | |
|---|---|
| Investigational medicinal product name | Clofarabine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate and solvent for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:
40 mg/m2/d x 5 d

| | |
|---|---|
| Investigational medicinal product name | DaunoXome |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate and solvent for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:
80 mg/m2/d 1-3-5

| | |
|---|---|
| Investigational medicinal product name | Cytarabine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate and solvent for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:
2 gr/m2/d x 5 d

| **Number of subjects in period 1** | Dose level 1 | Dose level 2 | Dose level 3a |
|---|---|---|---|
| Started | 4 | 3 | 6 |
| Completed | 4 | 3 | 6 |

| **Number of subjects in period 1** | Dose level 3b | Dose level 4 | Dose level 5 |
|---|---|---|---|
| Started | 6 | 10 | 5 |
| Completed | 6 | 10 | 5 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | overall trial |

Reporting group description: -

| Reporting group values | overall trial | Total | |
|---|---|---|---|
| Number of subjects | 34 | 34 | |
| Age categorical | | | |
| paediatric patients | | | |
| Units: Subjects | | | |
| Infants and toddlers (28 days-23 months) | 6 | 6 | |
| Children (2-11 years) | 16 | 16 | |
| Adolescents (12-17 years) | 10 | 10 | |
| Adults (18-64 years) | 2 | 2 | |
| Gender categorical | | | |
| gender | | | |
| Units: Subjects | | | |
| Female | 14 | 14 | |
| Male | 20 | 20 | |
| Disease status | | | |
| Disease status | | | |
| Units: Subjects | | | |
| early first relapse | 15 | 15 | |
| refractory first relapse | 11 | 11 | |
| second relapse | 7 | 7 | |
| greater than second relapse | 1 | 1 | |
| FLT3/ITD | | | |
| FLT3/ITD mutated | | | |
| Units: Subjects | | | |
| no | 23 | 23 | |
| yes | 4 | 4 | |
| ND | 7 | 7 | |
| AML/ETO | | | |
| AML/ETO mutated | | | |
| Units: Subjects | | | |
| no | 25 | 25 | |
| yes | 0 | 0 | |
| ND | 9 | 9 | |
| CBFb-MYH11 | | | |
| CBFb-MYH11 mutated | | | |
| Units: Subjects | | | |
| no | 27 | 27 | |
| yes | 0 | 0 | |
| ND | 7 | 7 | |
| SCT | | | |
| underwent SCT | | | |
| Units: Subjects | | | |

| | | | |
|---|---|---|---|
| no | 22 | 22 | |
| yes, 1 SCT | 11 | 11 | |
| yes, 2 SCT's | 1 | 1 | |
| WBC at initial diagnosis | | | |
| WBC at initial diagnosis | | | |
| Units: 10^9/L | | | |
| arithmetic mean | 58 | | |
| standard deviation | ± 108 | - | |
| WBC at inclusion | | | |
| WBC at inclusion | | | |
| Units: 10^9/L | | | |
| arithmetic mean | 19 | | |
| standard deviation | ± 60 | - | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Dose level 1 |
| Reporting group description: Clofarabine = 20 mg/m2/day x 5d, DaunoXome = 40 mg/m2/ d 1-3-5, Ara-C = 2 gr/m2/day x 5d | |
| Reporting group title | Dose level 2 |
| Reporting group description: Clofarabine = 30 mg/m2/day x 5d, DaunoXome = 40 mg/m2/ d 1-3-5, Ara-C = 2 gr/m2/day x 5d | |
| Reporting group title | Dose level 3a |
| Reporting group description: clofarabine = 30 mg/m2/day x 5d, DaunoXome = 60 mg/m2/ d 1-3-5, Ara-C = 2 gr/m2/day x 5d | |
| Reporting group title | Dose level 3b |
| Reporting group description: clofarabine = 30 mg/m2/day x 5d, DaunoXome = 60 mg/m2/ d 1-3-5, Ara-C = 2 gr/m2/day x 5d | |
| Reporting group title | Dose level 4 |
| Reporting group description: clofarabine = 40 mg/m2/day x 5d, DaunoXome = 60 mg/m2/ d 1-3-5, Ara-C = 2 gr/m2/day x 5d | |
| Reporting group title | Dose level 5 |
| Reporting group description: clofarabine = 40 mg/m2/day x 5d, DaunoXome = 80 mg/m2/ d 1-3-5, Ara-C = 2 gr/m2/day x 5d | |

### Primary: Safety and tolerability

| | |
|---|---|
| End point title | Safety and tolerability[1] |
| End point description: safety/tolerability was investigated by counting the DLT's per dose level | |
| End point type | Primary |
| End point timeframe: during first course | |

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: Study is phase I with primary endpoint DLT's ; number of DLT's is provided; statistical analysis not applicable.

| End point values | Dose level 1 | Dose level 2 | Dose level 3a | Dose level 3b |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 4 | 3 | 6 | 6 |
| Units: number of DLT's | 1 | 0 | 4 | 1 |

| End point values | Dose level 4 | Dose level 5 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 10 | 5 | | |
| Units: number of DLT's | 1 | 2 | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: OS

| End point title | OS |
|---|---|

End point description:

OS (overall survival)

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

End point timeframe:

OS = time from study inclusion to death/DLC

| End point values | Dose level 1 | Dose level 2 | Dose level 3a | Dose level 3b |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 4 | 3 | 6 | 6 |
| Units: months | | | | |
| alive | 0 | 0 | 1 | 2 |
| dead | 4 | 3 | 5 | 4 |

| End point values | Dose level 4 | Dose level 5 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 10 | 5 | | |
| Units: months | | | | |
| alive | 6 | 4 | | |
| dead | 4 | 1 | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: EFS

| End point title | EFS |
|---|---|

End point description:

event free survival

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

End point timeframe:
EFS = time from inclusion in study to treatment failure, relapse or death/DLC

| **End point values** | Dose level 1 | Dose level 2 | Dose level 3a | Dose level 3b |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 4 | 3 | 6 | 6 |
| Units: months | | | | |
| EFS | 0 | 0 | 0 | 2 |
| treat. failure | 3 | 1 | 4 | 0 |
| relapse | 0 | 2 | 1 | 1 |
| death | 1 | 0 | 1 | 3 |

| **End point values** | Dose level 4 | Dose level 5 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 10 | 5 | | |
| Units: months | | | | |
| EFS | 6 | 2 | | |
| treat. failure | 1 | 1 | | |
| relapse | 1 | 2 | | |
| death | 2 | 0 | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Response on cycle 1

| End point title | Response on cycle 1 |
|---|---|
| End point description:<br>response on first cycle | |
| End point type | Secondary |
| End point timeframe:<br>evaluation of first treatment cycle | |

| **End point values** | Dose level 1 | Dose level 2 | Dose level 3a | Dose level 3b |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 4 | 3 | 6 | 6 |
| Units: type respose | | | | |
| CR | 0 | 0 | 0 | 0 |
| CRi | 1 | 2 | 1 | 5 |
| PR | 0 | 0 | 0 | 0 |

| | | | | |
|---|---|---|---|---|
| SD | 1 | 0 | 3 | 0 |
| PD | 1 | 0 | 1 | 0 |
| treatment failure | 0 | 1 | 0 | 0 |
| unknown | 0 | 0 | 1 | 1 |

| **End point values** | Dose level 4 | Dose level 5 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 10 | 5 | | |
| Units: type respose | | | | |
| CR | 2 | 3 | | |
| CRi | 5 | 1 | | |
| PR | 1 | 0 | | |
| SD | 1 | 1 | | |
| PD | 0 | 0 | | |
| treatment failure | 0 | 0 | | |
| unknown | 1 | 0 | | |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Response on cycle 2**

| End point title | Response on cycle 2 |
|---|---|
| End point description:<br>response on second cycle | |
| End point type | Secondary |
| End point timeframe:<br>evaluation of second treatment cycle | |

| **End point values** | Dose level 1 | Dose level 2 | Dose level 3a | Dose level 3b |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 4 | 3 | 6 | 6 |
| Units: type response | | | | |
| CR | 0 | 0 | 0 | 0 |
| CRi | 0 | 0 | 0 | 0 |
| PR | 0 | 0 | 0 | 0 |
| SD | 0 | 0 | 0 | 0 |
| PD | 0 | 0 | 0 | 0 |
| treatment failure | 0 | 0 | 0 | 0 |
| unknown | 4 | 3 | 6 | 6 |

| End point values | Dose level 4 | Dose level 5 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 10 | 5 | | |
| Units: type response | | | | |
| CR | 0 | 0 | | |
| CRi | 2 | 0 | | |
| PR | 0 | 0 | | |
| SD | 0 | 0 | | |
| PD | 0 | 0 | | |
| treatment failure | 0 | 0 | | |
| unknown | 8 | 5 | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse event assessment from time of signing informed consent until long term follow-up.

Adverse event reporting additional description:

(S)AEs need to be reported until 30 days after the last administration of study medication, or until another treatment regimen is started, whichever occurs first. However, in the case of AEs occurring later than this deadline but which are considered related to the study medication by the investigator, such AEs still need to be reported.

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

### Dictionary used

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

### Reporting groups

| | |
|---|---|
| Reporting group title | dose level 1-5 |

Reporting group description:

all patients treated in dose levels 1-5

| **Serious adverse events** | dose level 1-5 | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 26 / 34 (76.47%) | | |
| number of deaths (all causes) | 21 | | |
| number of deaths resulting from adverse events | 2 | | |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 15 / 34 (44.12%) | | |
| occurrences causally related to treatment / all | 13 / 15 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| blood/BM other: progressive leukemia | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Gastrointestinal disorders | | | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diarrhoea | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| hypoxia | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Skin and subcutaneous tissue disorders | | | |
| rash | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Endocrine disorders | | | |
| Capillary disorder | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| infection lung | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infection | | | |
| subjects affected / exposed | 6 / 34 (17.65%) | | |
| occurrences causally related to treatment / all | 4 / 6 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| **Non-serious adverse events** | dose level 1-5 | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 34 / 34 (100.00%) | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |

| | | | |
|---|---|---|---|
| Tumor lysis syndrome | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Vascular disorders | | | |
| Capillary leak syndrome | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| General disorders and administration site conditions | | | |
| Fever | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |
| subjects affected / exposed | 2 / 34 (5.88%) | | |
| occurrences (all) | 2 | | |
| Pain bone | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Pain (headache) | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Pain oral cavity | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Pain-legs/feet | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Immune system disorders | | | |
| Allergic reaction (abelcet) | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Hypoxia | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |
| subjects affected / exposed | 2 / 34 (5.88%) | | |
| occurrences (all) | 3 | | |
| Pneumonitis | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 2 | | |
| Dyspnea | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Investigations | | | |
| Hyperbillirubinemia | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Bilirubin | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| ALT | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Glutamyl transpeptidase | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| PTT | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| GGT | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Hypokalaemia | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Cardiac disorders | | | |
| Hypotension | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |
| subjects affected / exposed | 2 / 34 (5.88%) | | |
| occurrences (all) | 3 | | |
| Hypertension | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Ventricular tachycardia | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Nervous system disorders | | | |
| Tremor | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Blood and lymphatic system disorders | | | |
| Platelets | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |
| subjects affected / exposed | 4 / 34 (11.76%) | | |
| occurrences (all) | 9 | | |
| Anemia | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |
| subjects affected / exposed | 2 / 34 (5.88%) | | |
| occurrences (all) | 3 | | |
| DIC | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |
| subjects affected / exposed | 2 / 34 (5.88%) | | |
| occurrences (all) | 2 | | |
| Thrombocytopenia | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |
| subjects affected / exposed | 2 / 34 (5.88%) | | |
| occurrences (all) | 2 | | |
| Neutropenia | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |
| subjects affected / exposed | 4 / 34 (11.76%) | | |
| occurrences (all) | 4 | | |
| Hemoglobin | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |
| subjects affected / exposed | 4 / 34 (11.76%) | | |
| occurrences (all) | 4 | | |
| Leukocytes | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |
| subjects affected / exposed | 3 / 34 (8.82%) | | |
| occurrences (all) | 5 | | |
| Edema limb | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Neutrophiles | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Eye disorders | | | |
| Dry eye syndrome | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Ocular/other hyposfagma, swelling | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Gastrointestinal disorders | | | |
| Vomiting | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |
| subjects affected / exposed | 3 / 34 (8.82%) | | |
| occurrences (all) | 3 | | |
| Nausea | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |
| subjects affected / exposed | 5 / 34 (14.71%) | | |
| occurrences (all) | 5 | | |
| Diarrhea | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |
| subjects affected / exposed | 6 / 34 (17.65%) | | |
| occurrences (all) | 6 | | |
| Anorexia | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |
| subjects affected / exposed | 2 / 34 (5.88%) | | |
| occurrences (all) | 2 | | |
| Dehydration | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Abdominal pain | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |
| subjects affected / exposed | 2 / 34 (5.88%) | | |
| occurrences (all) | 2 | | |
| Ascites | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Skin and subcutaneous tissue disorders | | | |
| Pruritus | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |
| subjects affected / exposed | 2 / 34 (5.88%) | | |
| occurrences (all) | 2 | | |
| Rash: Hand - feet skin reaction | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Skin pain (cellulitis) | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Renal and urinary disorders | | | |
| Acute renal failure | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 2 | | |
| Reduced diuresis | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Infections and infestations | | | |
| Infection | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |
| subjects affected / exposed | 2 / 34 (5.88%) | | |
| occurrences (all) | 3 | | |
| Febrile neutropenia | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |
| subjects affected / exposed | 19 / 34 (55.88%) | | |
| occurrences (all) | 36 | | |
| Infection with grade 3 or 4 neutrophils (sepsis) | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |
| subjects affected / exposed | 2 / 34 (5.88%) | | |
| occurrences (all) | 2 | | |
| Infection lung | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Fever | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Infection documented clinically blood | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Sepsis Candides non Albicans | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Febrile Aplasia | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Infection (candida) | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Cellulitis infection | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Infection eyes with grade 4 ANC | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Infection - ANC grade 4 (CVAD) | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| AST | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Infection lungs | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Pulmonary infection (aspergillosis) | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Metabolism and nutrition disorders | | | |

| | | | |
|---|---|---|---|
| Acidosis | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Hypophosphataemia | Additional description: All grade 3 and grade 4 AE's related to the first treatment cycle | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 05 November 2011 | Revision of in- and exclusion criteria of the protocol regarding:<br>- uncontrolled infections: actively excluding patients who may have subclinical fungal infection;<br>- early relapse AML patients are eligible due to closure of the AML 2001-01 study;<br><br>Revision of the dose escalation schedule;<br>Prolongation of inclusion period;<br>Recalculation of Statistical approach and Sample size. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

### Online references

http://www.ncbi.nlm.nih.gov/pubmed/29773602