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: 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: 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: 2 gr/m2/d x 5d	
Arm title	Dose level 3a
Arm description: 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: 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: 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: 2 gr/m2/d x 5 d	
Arm title	Dose level 3b
Arm description: 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: 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: 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: 2 gr/m2/d x 5 d	
Arm title	Dose level 4
Arm description: 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: 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: 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: 2 gr/m2/d x 5 d	
Arm title	Dose level 5
Arm description: 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: response on first cycle	
End point type	Secondary
End point timeframe: 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: response on second cycle	
End point type	Secondary
End point timeframe: 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		

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: - uncontrolled infections: actively excluding patients who may have subclinical fungal infection; - early relapse AML patients are eligible due to closure of the AML 2001-01 study; Revision of the dose escalation schedule; Prolongation of inclusion period; 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