Clinical trial results:
Randomized Phase III Study of Low-Dose Cytarabine and Etoposide with or without All-Trans Retinoic Acid in Older Patients not Eligible for Intensive Chemotherapy with Acute Myeloid Leukemia and NPM1 Mutation

Summary

EudraCT number	2010-023409-37
Trial protocol	DE AT
Global end of trial date	13 July 2018

Results information

Result version number	v1 (current)
This version publication date	26 July 2019
First version publication date	26 July 2019

Trial information

Trial identification

Sponsor protocol code	AMLSG_15-10

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01237808
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University Hospital of Ulm
Sponsor organisation address	Albert-Einstein-Allee 23, Ulm, Germany, 89081
Public contact	AMLSG Clinical Trials Office, University Hospital Ulm, +49 731500 56072, aml.sekretariat@uniklinik-ulm.de
Scientific contact	AMLSG Clinical Trials Office, University Hospital Ulm, +49 731500 56072, aml.sekretariat@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	21 June 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 July 2018
Global end of trial reached?	Yes
Global end of trial date	13 July 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary Efficacy Objective
- Evaluation of overall survival after treatment with low-dose cytarabine and etoposide with or without all-trans retinoic acid (ATRA) in patients with acute myeloid leukemia (AML) and nucleophosmin-1 (NPM1) mutation ineligible for intensive treatment
Secondary Efficacy Objectives
-Evaluation of efficacy based on complete remission (CR) rates, event-free survival (EFS), and cumulative incidences of relapse and deaths in CR
Safety Objectives and QOL Objectives
- Evaluation of safety based on toxicity
- Evaluation of safety based on duration of neutropenia and leukopenia after each treatment cycle, incidence of infections, duration of hospitalization
-Assessment of quality of life

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	11 May 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 10
Country: Number of subjects enrolled	Germany: 134
Worldwide total number of subjects	144
EEA total number of subjects	144

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0

Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	2
From 65 to 84 years	136
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

First Patient in: 11.05.2011
Last Patient in: 14.09.2016
Recruitment was not interrupted during the course of the trial.

Pre-assignment

Screening details:

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

Pre-assignment period milestones

Number of subjects started	144
Number of subjects completed	144[1]

Notes:

[1] - The number of subjects reported to be in the pre-assignment period is not consistent with the number starting period 1. It is expected that the number completing the pre-assignment period are also present in the arms in period 1.
Justification: Two Analysis data sets were defined:
1. ITT (Intention to treat): included all randomized patients with signed informed consent. They were analyzed according to randomisation arm. (control: n=72, ATRA: n=72)
2. Safety: Analyses were performed according to the Treatment the patients actually received. Therefore, 6 patients did not receive the IMP in the ATRA arm and were analyzed for safety within the control arm. (control: n=78, ATRA: n=66)

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	Arm A: Control

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Cytarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

During six repetitive treatment cycles:
Cytarabine 20 mg/day, s.c., bid, days 1-7; (total dose 280 mg).

Investigational medicinal product name	Etoposide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection, Capsule
Routes of administration	Intravenous use, Intravenous bolus use , Oral use

Dosage and administration details:

First Treatment cycle:
50 mg/m²/day, continuously i.v., days 1-3; (total dose 150 mg/m2).

Treatment cycle 2 to 6:
100 mg/day, p.o. or i.v. (over 1 hour), days 1-3; (total dose 300 mg).

Arm title	Arm B: ATRA
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Cytarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

During six repetitive treatment cycles:
Cytarabine 20 mg/day, s.c., bid, days 1-7; (total dose 280 mg).

Investigational medicinal product name	Etoposide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Concentrate for solution for infusion
Routes of administration	Intravenous bolus use , Intravenous use, Oral use

Dosage and administration details:

First Treatment cycle:
50 mg/m²/day, continuously i.v., days 1-3; (total dose 150 mg/m2).
Treatment cycle 2 to 6:
100 mg/day, p.o. or i.v. (over 1 hour), days 1-3; (total dose 300 mg).

Investigational medicinal product name	All-trans retinoic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

During six Treatment cycles:
45 mg/m²/day p.o., days 8-10;
15 mg/m²/day p.o., days 11-28
with or shortly after meals distributed on 3 doses per day

Number of subjects in period 1[2]	Arm A: Control	Arm B: ATRA
Started	72	72
Completed	32	11
Not completed	46	61
Adverse event, non-fatal	1	2
Other	5	6
Death	6	16
Patient wish	5	7
Lack of efficacy	29	30

Joined	6	0
Transferred in from other group/arm	6	-

Notes:

[2] - The number of subjects transferring in and out of the arms in the period are not the same. It is expected the net number of transfers in and out of the arms in a period, will be zero.

Justification: Two Analysis data sets were defined:
1. ITT (Intention to treat): included all randomized patients with signed informed consent. They were analyzed according to randomisation arm. (control: n=72, ATRA: n=72)
2. Safety: Analyses were performed according to the Treatment the patients actually received. Therefore, 6 patients did not receive the IMP in the ATRA arm and were analyzed for safety within the control arm. (control: n=78, ATRA: n=66)

Baseline characteristics

Reporting groups[1]	
Reporting group title	overall trial
Reporting group description: -	

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.
Justification: Two Analysis data sets were defined:
1. ITT (Intention to treat): included all randomized patients with signed informed consent. They were analyzed according to randomisation arm. (control: n=72, ATRA: n=72)
2. Safety: Analyses were performed according to the Treatment the patients actually received. Therefore, 6 patients did not receive the IMP in the ATRA arm and were analyzed for safety within the control arm. (control: n=78, ATRA: n=66)

Reporting group values	overall trial	Total	
Number of subjects	144	144	
Age categorical 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 Units: years			
median	76.8		
full range (min-max)	63.8 to 91.8	-	
Gender categorical Units: Subjects			
Female	70	70	
Male	74	74	
FLT3 ITD Units: Subjects			
negative	105	105	
positive	39	39	
ECOG performance status Units: Subjects			
level 0	21	21	
level 1	68	68	
level 2	41	41	
level 3	14	14	
level 4	0	0	
HCT-CI score Units: Subjects			
Score <=1	47	47	

Score 2	25	25	
Score 3	35	35	
Score >=4	37	37	
Type of AML Units: Subjects			
deNovo	126	126	
sAML	5	5	
tAML	13	13	
White blood count (WBC) Units: G/l median full range (min-max)		 -	
Platelets Units: G/l median full range (min-max)		 -	
Hemoglobin Units: g/dl median full range (min-max)		 -	
Blasts in peripheral blood Units: % (percent) median full range (min-max)	 28.5 0 to 98	 -	
Blasts in bone marrow Units: % (percent) median full range (min-max)		 -	
LDH Units: G/l median full range (min-max)		 -	

Subject analysis sets

Subject analysis set title	ITT population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The Intention to treat (ITT) population was defined according to the intent-to-treat principle and consists of all randomized patients with a signed informed consent. Patients in this population were analyzed according to the treatment arm assigned at randomization.

Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population included patients from the ITT population who actually received at least one dose or part of a dose of the study treatments (low-dose cytarabine and etoposide/etoposidphosphate with or without all-trans retinoic acid (ATRA)) during the considered treatment phase. The safety population was the primary population for the analysis of safety parameters. All analyses using this population were based on the treatment actually received.

Reporting group values	ITT population	Safety Population	
Number of subjects	144	144	
Age categorical 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 Units: years			
median	76.8	76.8	
full range (min-max)	63.8 to 91.8	63.8 to 91.8	
Gender categorical Units: Subjects			
Female	70	70	
Male	74	74	
FLT3 ITD Units: Subjects			
negative	105	105	
positive	39	39	
ECOG performance status Units: Subjects			
level 0	21	21	
level 1	68	68	
level 2	41	41	
level 3	14	14	
level 4	0	0	
HCT-CI score Units: Subjects			
Score <=1	47	47	
Score 2	25	25	
Score 3	35	35	
Score >=4	37	37	
Type of AML Units: Subjects			
deNovo	126	126	
sAML	5	5	
tAML	13	13	
White blood count (WBC) Units: G/l			
median	20.4		
full range (min-max)	0.4 to 335.0		
Platelets Units: G/l			
median	66		

full range (min-max)	4 to 494		
Hemoglobin Units: g/dl			
median	9.1		
full range (min-max)	5.2 to 13.2		
Blasts in peripheral blood Units: % (percent)			
median	28.5	28.5	
full range (min-max)	0 to 98	0 to 98	
Blasts in bone marrow Units: % (percent)			
median	80		
full range (min-max)	5 to 100		
LDH Units: G/l			
median	397.5		
full range (min-max)	155 to 2111		

End points

End points reporting groups

Reporting group title	Arm A: Control
Reporting group description: -	
Reporting group title	Arm B: ATRA
Reporting group description: -	
Subject analysis set title	ITT population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The Intention to treat (ITT) population was defined according to the intent-to-treat principle and consists of all randomized patients with a signed informed consent. Patients in this population were analyzed according to the treatment arm assigned at randomization.

Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population included patients from the ITT population who actually received at least one dose or part of a dose of the study treatments (low-dose cytarabine and etoposide/etoposidphosphate with or without all-trans retinoic acid (ATRA)) during the considered treatment phase. The safety population was the primary population for the analysis of safety parameters. All analyses using this population were based on the treatment actually received.

Primary: Overall survival

End point title	Overall survival

End point description:

The primary efficacy endpoint was OS, which was defined as the time from the date of randomization to the date of death due to any cause. For patients who are still alive and patients who are lost to follow up, OS was be censored at the date they were last known to be alive.

End point type	Primary

End point timeframe:

after two years

End point values	Arm A: Control	Arm B: ATRA	ITT population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	72	72	144	
Units: Median overall survival				
median (confidence interval 95%)	9.15 (7.38 to 12.52)	5.02 (3.61 to 7.61)	6.56 (5.15 to 9.31)	

Attachments (see zip file)	Overall survival/AG-oscurve_all-2.jpg

Statistical analyses

Statistical analysis title	Log rank test
Comparison groups	Arm B: ATRA v Arm A: Control

Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.023 [1]
Method	Logrank

Notes:

[1] - There were significant differences between the treatment groups with the ATRA group performing worse than the control group: chisq=5.15 on 1 degrees of freedom, p=0.023.

Secondary: Rate of complete Remission (CR/CRi)

End point title	Rate of complete Remission (CR/CRi)

End point description:

A patient was said to have achieved CR/CRi during the overall study treatment if his/her best response during or at completion of the study treatment was a CR/CRi; all other patients who did not meet this criterion were considered not to have achieved CR/CRi during treatment and regarded as having events at Day 1 after start of treatment.

End point type	Secondary

End point timeframe:

6 months

End point values	Arm A: Control	Arm B: ATRA	ITT population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	72	72	72	
Units: Subjects with complete remission	26	24	50	

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative incidence of relapse

End point title	Cumulative incidence of relapse

End point description:

The analyses of CIR and CID were restricted to patients who achieved CR/CRi during study treatment. For patients not experiencing relapse or death during the study, CIR and CID were censored at the date of last response evaluation. The incidence of relapse was estimated using the cumulative incidence function, treating death in first CR/CRi as a competing risk. Non-relapse mortality was analyzed in the same way, treating relapse in first CR/CRi as a competing risk.

End point type	Secondary

End point timeframe:

2 years

End point values	Arm A: Control	Arm B: ATRA	ITT population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	26	24	50	
Units: CIR after two years				
number (confidence interval 95%)	0.92 (0.82 to 1.00)	0.88 (0.74 to 1.00)	0.90 (0.83 to 0.98)	

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative incidence of death

End point title	Cumulative incidence of death

End point description:

The analyses of CIR and CID were restricted to patients who achieved CR/CRi during study treatment. For patients not experiencing relapse or death during the study, CIR and CID were censored at the date of last response evaluation. The incidence of relapse was estimated using the cumulative incidence function, treating death in first CR/CRi as a competing risk. Non-relapse mortality was analyzed in the same way, treating relapse in first CR/CRi as a competing risk.

End point type	Secondary

End point timeframe:

2 years

End point values	Arm A: Control	Arm B: ATRA	ITT population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	26	24	50	
Units: CID after 2 years				
number (confidence interval 95%)	0.00 (0.00 to 0.00)	0.08 (0.00 to 0.19)	0.04 (0.00 to 0.09)	

Statistical analyses

No statistical analyses for this end point

Secondary: Event-free survival

End point title	Event-free survival

End point description:

Event-free survival (EFS) was defined as the time from the date of entry into the trial to the date of either primary refractory disease, relapse from CR/CRi or death from any cause. Refractory disease described the failure to achieve CR/CRi within study

End point type	Secondary

End point timeframe:

2 years

End point values	Arm A: Control	Arm B: ATRA	ITT population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	72	72	144	
Units: months				
median (confidence interval 95%)	0.13 (0.07 to 1.08)	0.16 (0.10 to 1.02)	0.16 (0.10 to 0.62)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Quality of life (global health status)

End point title	Quality of life (global health status)

End point description:

After evaluation of EORTC (European Organisation for Research and Treatment of Cancer) Quality of Life Core Questionnaire (QLQ-C30), scores were derived.
All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level.
Changes in score values between diagnosis and end of Treatment were analyzed.

End point type	Other pre-specified

End point timeframe:

6 months

End point values	Arm A: Control	Arm B: ATRA	ITT population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	7	7	14	
Units: Changes in score value %				
median (full range (min-max))	16.7 (-16.7 to 58.3)	16.7 (-33.3 to 66.7)	16.7 (-33.3 to 66.7)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Rate of Early/Hypoplastic Deaths (ED/HD)

End point title	Rate of Early/Hypoplastic Deaths (ED/HD)

End point description:

End point type	Other pre-specified

End point timeframe:

6 months

End point values	Arm A: Control	Arm B: ATRA	ITT population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	78	66	144	
Units: Number of ED/HD	10	9	19	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Incidence of infection after each treatment cycle

End point title	Incidence of infection after each treatment cycle

End point description:

End point type	Other pre-specified

End point timeframe:

6 months

End point values	Arm A: Control	Arm B: ATRA	Safety Population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	78	66	144	
Units: Incidence, %				
number (confidence interval 95%)				
Cycle 1	57.7 (46.6 to 68.0)	60.6 (48.5 to 71.5)	59.0 (50.9 to 66.7)	
Cycle 2	31.9 (20.4 to 46.2)	58.5 (43.4 to 72.2)	44.3 (34.4 to 54.7)	
Cycle 3	23.1 (12.6 to 38.3)	33.3 (18.0 to 53.3)	27.0 (17.6 to 39.0)	
Cycle 4	11.7 (4.7 to 26.7)	22.2 (9.0 to 45.2)	15.4 (8.0 to 27.5)	
Cycle 5	16.1 (7.1 to 32.6)	18.8 (6.6 to 43.0)	17.0 (8.9 to 30.1)	
Cycle 6	7.7 (2.1 to 24.1)	16.7 (4.7 to 44.8)	10.5 (4.2 to 24.1)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Duration of neutropenia

End point title	Duration of neutropenia

End point description:

End point type	Other pre-specified

End point timeframe:
6 months

End point values	Arm A: Control	Arm B: ATRA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	66		
Units: Days				
median (confidence interval 95%)				
Cycle 1	28 (26 to 38)	29 (24 to 34)		
Cycle 2	27 (25 to 34)	30 (22 to 36)		
Cycle 3	25 (17 to 30)	32 (28 to 32)		
Cycle 4	27 (27 to 27)	24 (21 to 24)		
Cycle 5	28 (27 to 28)	34 (27 to 34)		
Cycle 6	27 (22 to 27)	40 (40 to 40)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Duration of thrombopenia

End point title	Duration of thrombopenia

End point description:

End point type	Other pre-specified

End point timeframe:
6 months

End point values	Arm A: Control	Arm B: ATRA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	66		
Units: Days				
median (confidence interval 95%)				
Cycle 1	18 (17 to 21)	24 (20 to 33)		
Cycle 2	16 (15 to 21)	20 (18 to 35)		
Cycle 3	16 (12 to 16)	28 (17 to 28)		
Cycle 4	24 (17 to 24)	32 (23 to 32)		
Cycle 5	18 (12 to 18)	18 (18 to 18)		
Cycle 6	17 (4 to 17)	40 (40 to 40)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of nights in hospital (initial stay)

End point title	Number of nights in hospital (initial stay)

End point description:

End point type	Other pre-specified

End point timeframe:

6 months

End point values	Arm A: Control	Arm B: ATRA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	66		
Units: Nights				
median (full range (min-max))				
Cycle 1	21 (1 to 43)	21 (0 to 53)		
Cycle 2	8 (0 to 34)	9 (0 to 39)		
Cycle 3	7 (0 to 34)	7 (0 to 13)		
Cycle 4	6 (0 to 29)	7 (0 to 13)		
Cycle 5	6 (0 to 10)	7 (0 to 11)		
Cycle 6	4 (0 to 16)	6 (0 to 9)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events were reported from Inform Consent signature up to 28 days after last study drug administration or until all drug-related toxicities had been resolved, whichever was late.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	3.0

Reporting groups

Reporting group title	Arm A: Control
Reporting group description: -	
Reporting group title	Arm B: ATRA

Reporting group description: -

Serious adverse events	Arm A: Control	Arm B: ATRA	
Total subjects affected by serious adverse events			
subjects affected / exposed	45 / 78 (57.69%)	40 / 66 (60.61%)	
number of deaths (all causes)	12	16	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Secondary malignancy			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
CNS Hemorrhage			
subjects affected / exposed	1 / 78 (1.28%)	2 / 66 (3.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Thrombosis/thrombus/embolism			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Intra-operative injury: Retina			

subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Constitutional symptoms - other			
subjects affected / exposed	4 / 78 (5.13%)	3 / 66 (4.55%)	
occurrences causally related to treatment / all	1 / 4	1 / 3	
deaths causally related to treatment / all	1 / 2	0 / 2	
Fever			
subjects affected / exposed	1 / 78 (1.28%)	2 / 66 (3.03%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	3 / 78 (3.85%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 3	1 / 1	
deaths causally related to treatment / all	0 / 3	1 / 1	
Pain -other			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Hemorrhage pulmonary			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
ARDS			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dyspnea			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hypoxia			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	2 / 78 (2.56%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary -other			
subjects affected / exposed	1 / 78 (1.28%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	1 / 1	
Cardiac disorders			
Cardiac Arrhythmia - Other			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular arrhythmia			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac general - other			
subjects affected / exposed	2 / 78 (2.56%)	2 / 66 (3.03%)	
occurrences causally related to treatment / all	0 / 1	2 / 4	
deaths causally related to treatment / all	0 / 0	1 / 2	
Cardiac ischemia/infarction			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular dysfunction			

subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
CNS ischemia			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mood alteration			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurology - Other			
subjects affected / exposed	4 / 78 (5.13%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 78 (1.28%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope (fainting)			
subjects affected / exposed	1 / 78 (1.28%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head/Headache			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			

Hemoglobin			
subjects affected / exposed	2 / 78 (2.56%)	2 / 66 (3.03%)	
occurrences causally related to treatment / all	7 / 7	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytes			
subjects affected / exposed	2 / 78 (2.56%)	2 / 66 (3.03%)	
occurrences causally related to treatment / all	8 / 8	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophils			
subjects affected / exposed	3 / 78 (3.85%)	3 / 66 (4.55%)	
occurrences causally related to treatment / all	4 / 4	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelets			
subjects affected / exposed	3 / 78 (3.85%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumor lysis syndrome			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhea			
subjects affected / exposed	0 / 78 (0.00%)	3 / 66 (4.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
GI -other			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Nausea			

subjects affected / exposed	1 / 78 (1.28%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemorrhage, GI			
subjects affected / exposed	1 / 78 (1.28%)	2 / 66 (3.03%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Stomach pain			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatology -Other			
subjects affected / exposed	1 / 78 (1.28%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injection site reaction			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Hemorrhage, GU			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal - other			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			

subjects affected / exposed	3 / 78 (3.85%)	5 / 66 (7.58%)	
occurrences causally related to treatment / all	3 / 3	4 / 5	
deaths causally related to treatment / all	1 / 1	0 / 0	
Stricture anastomotic, GU			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Fracture			
subjects affected / exposed	1 / 78 (1.28%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal - Other			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Febrile neutroopenia			
subjects affected / exposed	6 / 78 (7.69%)	11 / 66 (16.67%)	
occurrences causally related to treatment / all	5 / 6	10 / 14	
deaths causally related to treatment / all	0 / 0	2 / 2	
Gastrointestinal: Esophagus			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection - other			
subjects affected / exposed	4 / 78 (5.13%)	2 / 66 (3.03%)	
occurrences causally related to treatment / all	2 / 4	1 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	

Sepsis			
subjects affected / exposed	3 / 78 (3.85%)	4 / 66 (6.06%)	
occurrences causally related to treatment / all	2 / 3	3 / 4	
deaths causally related to treatment / all	1 / 1	2 / 3	
Infection with grade 3 or 4 neutrophils			
subjects affected / exposed	4 / 78 (5.13%)	2 / 66 (3.03%)	
occurrences causally related to treatment / all	3 / 4	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal: joint			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal: Soft tissue			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung (pneumonia)			
subjects affected / exposed	11 / 78 (14.10%)	5 / 66 (7.58%)	
occurrences causally related to treatment / all	6 / 11	2 / 6	
deaths causally related to treatment / all	1 / 3	0 / 1	
Urinary tract NOS			
subjects affected / exposed	2 / 78 (2.56%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm A: Control	Arm B: ATRA	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	77 / 78 (98.72%)	64 / 66 (96.97%)	
Vascular disorders			
Hemorrhage - other			
subjects affected / exposed	5 / 78 (6.41%)	5 / 66 (7.58%)	
occurrences (all)	6	8	

Edema: limb			
subjects affected / exposed	12 / 78 (15.38%)	15 / 66 (22.73%)	
occurrences (all)	19	21	
Phlebitis			
subjects affected / exposed	5 / 78 (6.41%)	4 / 66 (6.06%)	
occurrences (all)	5	5	
Cardiac disorders			
Cardiac general - other			
subjects affected / exposed	5 / 78 (6.41%)	4 / 66 (6.06%)	
occurrences (all)	8	6	
Hypertension			
subjects affected / exposed	18 / 78 (23.08%)	10 / 66 (15.15%)	
occurrences (all)	36	14	
Hypotension			
subjects affected / exposed	4 / 78 (5.13%)	3 / 66 (4.55%)	
occurrences (all)	4	4	
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 78 (6.41%)	5 / 66 (7.58%)	
occurrences (all)	7	5	
Mood alteration			
subjects affected / exposed	6 / 78 (7.69%)	2 / 66 (3.03%)	
occurrences (all)	13	3	
Mood alteration: agitation			
subjects affected / exposed	5 / 78 (6.41%)	2 / 66 (3.03%)	
occurrences (all)	7	2	
Mood alteration: Depression			
subjects affected / exposed	2 / 78 (2.56%)	5 / 66 (7.58%)	
occurrences (all)	2	6	
Head/Headache			
subjects affected / exposed	5 / 78 (6.41%)	8 / 66 (12.12%)	
occurrences (all)	5	11	
Blood and lymphatic system disorders			
Blood - other			
subjects affected / exposed	4 / 78 (5.13%)	4 / 66 (6.06%)	
occurrences (all)	4	4	
Hemoglobin			

subjects affected / exposed	63 / 78 (80.77%)	54 / 66 (81.82%)	
occurrences (all)	170	135	
Leukocytes			
subjects affected / exposed	52 / 78 (66.67%)	48 / 66 (72.73%)	
occurrences (all)	161	115	
Neutrophils			
subjects affected / exposed	39 / 78 (50.00%)	31 / 66 (46.97%)	
occurrences (all)	99	69	
Platelets			
subjects affected / exposed	65 / 78 (83.33%)	61 / 66 (92.42%)	
occurrences (all)	171	140	
General disorders and administration site conditions			
Constitutional symptoms - other			
subjects affected / exposed	9 / 78 (11.54%)	2 / 66 (3.03%)	
occurrences (all)	15	5	
Fatigue			
subjects affected / exposed	13 / 78 (16.67%)	14 / 66 (21.21%)	
occurrences (all)	33	22	
Fever			
subjects affected / exposed	26 / 78 (33.33%)	15 / 66 (22.73%)	
occurrences (all)	39	17	
Insomnia			
subjects affected / exposed	25 / 78 (32.05%)	18 / 66 (27.27%)	
occurrences (all)	41	23	
Weight gain			
subjects affected / exposed	9 / 78 (11.54%)	7 / 66 (10.61%)	
occurrences (all)	10	11	
Weight loss			
subjects affected / exposed	5 / 78 (6.41%)	2 / 66 (3.03%)	
occurrences (all)	6	2	
Pain NOS			
subjects affected / exposed	4 / 78 (5.13%)	4 / 66 (6.06%)	
occurrences (all)	8	4	
Pain			

subjects affected / exposed	14 / 78 (17.95%)	10 / 66 (15.15%)	
occurrences (all)	19	16	
Pain -other			
subjects affected / exposed	7 / 78 (8.97%)	8 / 66 (12.12%)	
occurrences (all)	12	11	
Gastrointestinal disorders			
Anorexia			
subjects affected / exposed	5 / 78 (6.41%)	7 / 66 (10.61%)	
occurrences (all)	10	7	
Constipation			
subjects affected / exposed	29 / 78 (37.18%)	17 / 66 (25.76%)	
occurrences (all)	51	19	
Diarrhea			
subjects affected / exposed	16 / 78 (20.51%)	9 / 66 (13.64%)	
occurrences (all)	21	12	
Hemorrhoids			
subjects affected / exposed	6 / 78 (7.69%)	2 / 66 (3.03%)	
occurrences (all)	8	3	
Mucositis (clinical exam)			
subjects affected / exposed	15 / 78 (19.23%)	9 / 66 (13.64%)	
occurrences (all)	21	9	
Mucositis (functional/symptomatic)			
subjects affected / exposed	6 / 78 (7.69%)	5 / 66 (7.58%)	
occurrences (all)	12	5	
Nausea			
subjects affected / exposed	29 / 78 (37.18%)	17 / 66 (25.76%)	
occurrences (all)	69	41	
Vomiting			
subjects affected / exposed	6 / 78 (7.69%)	9 / 66 (13.64%)	
occurrences (all)	6	10	
Abdomen NOS pain			
subjects affected / exposed	5 / 78 (6.41%)	5 / 66 (7.58%)	
occurrences (all)	8	7	
Stomach pain			
subjects affected / exposed	3 / 78 (3.85%)	4 / 66 (6.06%)	
occurrences (all)	3	5	

Respiratory, thoracic and mediastinal disorders			
Hemorrhage pulmonary			
subjects affected / exposed	5 / 78 (6.41%)	6 / 66 (9.09%)	
occurrences (all)	5	7	
Cough			
subjects affected / exposed	11 / 78 (14.10%)	11 / 66 (16.67%)	
occurrences (all)	12	13	
Dyspnea			
subjects affected / exposed	11 / 78 (14.10%)	11 / 66 (16.67%)	
occurrences (all)	15	14	
Pleural effusion			
subjects affected / exposed	3 / 78 (3.85%)	5 / 66 (7.58%)	
occurrences (all)	4	5	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	4 / 78 (5.13%)	3 / 66 (4.55%)	
occurrences (all)	13	8	
Dermatology -other			
subjects affected / exposed	10 / 78 (12.82%)	7 / 66 (10.61%)	
occurrences (all)	15	11	
Injection site reaction			
subjects affected / exposed	4 / 78 (5.13%)	6 / 66 (9.09%)	
occurrences (all)	4	7	
Rash			
subjects affected / exposed	13 / 78 (16.67%)	9 / 66 (13.64%)	
occurrences (all)	16	12	
Hematoma			
subjects affected / exposed	6 / 78 (7.69%)	3 / 66 (4.55%)	
occurrences (all)	7	3	
Petechiae			
subjects affected / exposed	4 / 78 (5.13%)	8 / 66 (12.12%)	
occurrences (all)	7	8	
Renal and urinary disorders			
Renal - other			
subjects affected / exposed	6 / 78 (7.69%)	1 / 66 (1.52%)	
occurrences (all)	8	1	

Fluid retention/edema			
subjects affected / exposed	16 / 78 (20.51%)	10 / 66 (15.15%)	
occurrences (all)	29	11	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	6 / 78 (7.69%)	3 / 66 (4.55%)	
occurrences (all)	8	3	
Extremity-limb pain			
subjects affected / exposed	6 / 78 (7.69%)	6 / 66 (9.09%)	
occurrences (all)	9	14	
Joint pain			
subjects affected / exposed	6 / 78 (7.69%)	2 / 66 (3.03%)	
occurrences (all)	13	2	
Infections and infestations			
Febrile neutropenia			
subjects affected / exposed	11 / 78 (14.10%)	10 / 66 (15.15%)	
occurrences (all)	16	17	
Infection - other			
subjects affected / exposed	13 / 78 (16.67%)	11 / 66 (16.67%)	
occurrences (all)	23	21	
Infection with grade 3 or 4 neutrophils			
subjects affected / exposed	5 / 78 (6.41%)	6 / 66 (9.09%)	
occurrences (all)	7	12	
Lung (pneumonia)			
subjects affected / exposed	11 / 78 (14.10%)	17 / 66 (25.76%)	
occurrences (all)	14	30	
Urinary tract NOS			
subjects affected / exposed	6 / 78 (7.69%)	4 / 66 (6.06%)	
occurrences (all)	6	4	
Metabolism and nutrition disorders			
Creatinine			
subjects affected / exposed	10 / 78 (12.82%)	4 / 66 (6.06%)	
occurrences (all)	18	6	
GGT			
subjects affected / exposed	2 / 78 (2.56%)	6 / 66 (9.09%)	
occurrences (all)	4	7	

Hyperuricemia			
subjects affected / exposed	11 / 78 (14.10%)	3 / 66 (4.55%)	
occurrences (all)	22	4	
Hypocalcemia			
subjects affected / exposed	8 / 78 (10.26%)	6 / 66 (9.09%)	
occurrences (all)	10	9	
Hypokalemia			
subjects affected / exposed	24 / 78 (30.77%)	19 / 66 (28.79%)	
occurrences (all)	39	32	
Metabolic: Other			
subjects affected / exposed	11 / 78 (14.10%)	10 / 66 (15.15%)	
occurrences (all)	19	14	
CRP increase			
subjects affected / exposed	4 / 78 (5.13%)	3 / 66 (4.55%)	
occurrences (all)	10	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 June 2014	Amendment 1 (dated 17 June 2014) was issued after enrolment of n=86 patients. The following major procedural changes were made to the protocol: • Dose reduction of ATRA: Administration of 45mg/m² from day 8 until day 10, thereafter from day 11 until day 28 reduction of ATRA dose to 15mg/m² (Integration of urgent amendment due to increased frequency of toxicities, in particular infections, and deaths observed in the ATRA arm compared to the control arm (Interim safety analysis, March 2014). • Changes in the personal responsibility
08 November 2016	Amendment 2 (dated 08 November 2016) to the protocol was issued after end of enrolment. The following major procedural changes were made to the protocol: • Integration of optional intravenous administration of Etoposide (cycles 2 to 6) due to a supply bottleneck of oral Etoposid (Vepesid K) and Etoposidphosphat (Etopophos). • Changes in the personal responsibility (coordinating investigator)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported