Clinical trial results:
Response-Adapted Sequential Azacitidine And Chemotherapy in Patients > 60 Years Old With Newly Diagnosed AML Eligible for Chemotherapy and allogeneic hematopoietic cell transplantation: A Multicentre Phase I/II study of the East German Hematology and Oncology Study Group (OSHO)

Summary

EudraCT number	2010-023584-17
Trial protocol	DE
Global end of trial date	25 May 2018

Results information

Result version number	v1 (current)
This version publication date	11 July 2020
First version publication date	11 July 2020
Summary attachment (see zip file)	final report Ras-Azic (RAS-AZIC_Ergebnisbericht_engl_final1.0_2019-05-08.pdf)

Trial information

Trial identification

Sponsor protocol code	RAS-AZIC

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	German Clinical Trial Register: DRKS00004519

Notes:

Sponsors

Sponsor organisation name	Universität Leipzig
Sponsor organisation address	Ritterstr. 26, Leipzig, Germany, 04109
Public contact	coordinating investigator, Universität Leipzig Department für Innere Medizin, 49 345 557 4909, ras-azic@zks.uni-leipzig.de
Scientific contact	coordinating investigator, Universität Leipzig Department für Innere Medizin, 49 345 557 4909, ras-azic@zks.uni-leipzig.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	08 May 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 May 2018
Global end of trial reached?	Yes
Global end of trial date	25 May 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Objectives of Phase I – Dose evaluation:
To investigate feasibility of azacitidine administered 75 mg/m2/day subcutaneously for 5 or 7 days followed by conventional AML induction chemotherapy in terms of dose limiting toxicity and to define the azacitidine total dose (5 or 7 days) per cycle to be administered in the phase II part of the trial.

Objectives of Phase II – Efficacy and safety:
To assess efficacy and safety of induction therapy with response-adapted sequential azacitidine and conventional AML induction chemotherapy in patients > 60 years with newly diagnosed AML (at the dose level resulting from the dose evaluation phase of the trial).
To assess efficacy in terms of the overall response rate (ORR) till day 90 including:
- Complete remissions (CR)
- Complete Remission with incomplete blood count recovery (CRi)
- Partial remissions (PR)

WE REPORT HERE THE RESULTS OF THE PHASE II PART OF THE TRIAL.

Protection of trial subjects:

Regular blood tests were conducted to determine the hematological and non-hematological toxicities.

Background therapy:

Hyperuricemia prophylaxis, eye bath and local glucocorticoides, if necessary: Serotonin (5-HT3) receptor antagonists (e.g., ondansetron), blood product support and myeloid growth factors (G-CSF)

Evidence for comparator:

No comparators used.

Actual start date of recruitment	13 December 2012
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	Germany: 112
Worldwide total number of subjects	112
EEA total number of subjects	112

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)	30
From 65 to 84 years	80
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

First patient in: 13.12.2012
Last patient in: 23.05.2016
Last patient last visit: 25.05.2018
Recruited number of patients: 114
Number of patients for final analysis: 109 enrolled on maximum tolerated dose

Pre-assignment

Screening details:

Only subjects who met all inclusion criteria, but none of the exclusion criteria were enrolled.

Period 1

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

Arms

Arm title	Azacitidine +/- induction chemo +/- azacitidine maintenance

Arm description:

In phase II all patients received azacitidine at the previously defined MTD (7 days) as initial therapy. According to the results of the bone marrow aspirate on day 15 of the first cycle of azacitidine, the patients received:
- Azacitidine (7 days) if blast count < 45%
- Induction chemotherapy if blast count >= 45%
Response assessment results on day 56 determined further therapy
- Azacitidine maintenance therapy up to two years after start of treatment in case of CR/CR
- Further induction chemotherapy in case of non CR/CRi, followed by azacitidine maintenance therapy if at least PR was achieved

Arm type	Experimental
Investigational medicinal product name	Azacitidine
Investigational medicinal product code	L01BC07
Other name	Vidaza
Pharmaceutical forms	Powder for suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

75 mg/m2 milligram(s)/square meter per day, days 1 to 7 (dose level 2), repeat d28

Investigational medicinal product name	Cytarabine
Investigational medicinal product code	L01BC01
Other name	ARA-cell
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1 g/m2/BID days 1,3,5,7 during induction cycle (up to two induction cycles)

Investigational medicinal product name	Mitoxantrone
Investigational medicinal product code	L01DB07
Other name	Mitoxantron
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

10 mg/m2/day days 1 to 3 during induction cycle (up to two induction cycles)

Number of subjects in period 1[1]	Azacitidine +/- induction chemo +/- azacitidine maintenance
Started	109
Completed	80
Not completed	29
Adverse event, serious fatal	9
Consent withdrawn by subject	2
Lost to follow-up	4
Lack of efficacy	14

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: This is a phase I dose-finding trial followed by a phase II trial. We report the phase II results, i.e. results on all patients treated on the maximum tolerated dose.

Baseline characteristics

Reporting groups	
Reporting group title	phase II

Reporting group description: -

Reporting group values	phase II	Total	
Number of subjects	109	109	
Age categorical Units: Subjects			
Adults (18-64 years)	30	30	
From 65-84 years	77	77	
85 years and over	2	2	
Age continuous Units: years			
median	70		
inter-quartile range (Q1-Q3)	64 to 74	-	
Gender categorical Units: Subjects			
Female	51	51	
Male	58	58	
AML diagnosis Units: Subjects			
primary AML	70	70	
secondary AML	38	38	
Other	1	1	
ECOG score Units: Subjects			
fully active	20	20	
able to carry out light work	71	71	
unable to carry out any work activities	17	17	
NA	1	1	
Leukocytes Units: Gpt/l			
median	4.3		
inter-quartile range (Q1-Q3)	1.9 to 24.4	-	
Absolute neutrophil count (ANC) Units: Gpt/l			
median	0.5		
inter-quartile range (Q1-Q3)	0.2 to 0.6	-	
Thrombocytes Units: Gpt/l			
median	64.5		
inter-quartile range (Q1-Q3)	38 to 114	-	
Haemoglobin Units: Gpt/l			
median	9		
inter-quartile range (Q1-Q3)	8.4 to 10.2	-	

End points

End points reporting groups

Reporting group title	Azacitidine +/- induction chemo +/- azacitidine maintenance

Reporting group description:

In phase II all patients received azacitidine at the previously defined MTD (7 days) as initial therapy. According to the results of the bone marrow aspirate on day 15 of the first cycle of azacitidine, the patients received:
- Azacitidine (7 days) if blast count < 45%
- Induction chemotherapy if blast count >= 45%
Response assessment results on day 56 determined further therapy
- Azacitidine maintenance therapy up to two years after start of treatment in case of CR/CR
- Further induction chemotherapy in case of non CR/CRi, followed by azacitidine maintenance therapy if at least PR was achieved

Primary: Overall response rate on day 90

End point title	Overall response rate on day 90[1]

End point description:

The primary endpoint was analyzed according to the optimal two-stage design. In addition, the overall response rate on day 90 has been estimated, and a 95% confidence interval was calculated.
Expected overall response rate of 61% with induction chemotherapy at day 90
Interim analysis after 40 patients: if <=19 CR/CRi/PR -> inferiority claimed, otherwise proceed
Final analysis after 109 patients: if <=57 CR/CRi/PR -> inferiority claimed, otherwise non-inferiority compared to standard induction

End point type	Primary

End point timeframe:

day 90

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: This is a single arm trial. Reporting of statistical analyses in this database require at least two arms, otherwise an error message occurs.

End point values	Azacitidine +/- induction chemo +/- azacitidine maintenance			
Subject group type	Reporting group			
Number of subjects analysed	109			
Units: yes / no				
CR/CRi/PR	70			
no response	39			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

Time from registration to death of any cause

End point type	Secondary

End point timeframe:

24 months

End point values	Azacitidine +/- induction chemo +/- azacitidine maintenance			
Subject group type	Reporting group			
Number of subjects analysed	109			
Units: months				
median (confidence interval 95%)	15.9 (12.9 to 18.9)			

Attachments (see zip file)	Overall Survival/OverallSurvival.JPG

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 is defined as time from enrolment to one of the following events:
- disease progression (according to IWG criteria),
- relapse after CR or CRi,
- death of any cause.

Subjects who dropped out or were alive at study termination had their overall survival times censored at the time of last contact, as appropriate.

End point type	Secondary

End point timeframe:

24 months

End point values	Azacitidine +/- induction chemo +/- azacitidine maintenance			
Subject group type	Reporting group			
Number of subjects analysed	109			
Units: months				
median (confidence interval 95%)	9.9 (7.7 to 12.0)			

Attachments (see zip file)	Event free survival/EventFreeSurvival.JPG

Statistical analyses

No statistical analyses for this end point

Secondary: Days alive and out of hospital up to d90

End point title	Days alive and out of hospital up to d90

End point description:

Every day a patient was alive and completely outside a hospital is counted. In case a patient was lost to follow-up before end of treatment, days after drop-out was not counted.

End point type	Secondary

End point timeframe:

90 days

End point values	Azacitidine +/- induction chemo +/- azacitidine maintenance			
Subject group type	Reporting group			
Number of subjects analysed	109			
Units: days				
median (inter-quartile range (Q1-Q3))	41.7 (24.5 to 59)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients undergoing hematopoietic stem cell transplantation

End point title	Number of patients undergoing hematopoietic stem cell transplantation

End point description:

End point type	Secondary

End point timeframe:

24 months

End point values	Azacitidine +/- induction chemo +/- azacitidine maintenance			
Subject group type	Reporting group			
Number of subjects analysed	109[2]			
Units: number				
patients with HCT	32			
patients without HCT	77			

Notes:

[2] - 20 patients underwent HCT while in 1st response, 12 after relapse

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: up to 28 days after last application of trial therapy	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups	
Reporting group title	Safety population

Reporting group description:

The safety population includes all enrolled patients who have received at least 1 dose of the trial medication, irrespective of their belonging to the phase I or phase II part of the trial. Patients were analyzed according to the treatment actually received. The safety population was used for all safety evaluations.

Serious adverse events	Safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	55 / 112 (49.11%)		
number of deaths (all causes)	67		
number of deaths resulting from adverse events	11		
Vascular disorders			
Shock haemorrhagic			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Thrombosis			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Multiple organ dysfunction syndrome			

subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pyrexia				
subjects affected / exposed	4 / 112 (3.57%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Dyspnoea				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	2 / 112 (1.79%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pulmonary oedema				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	5 / 112 (4.46%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 4			
Psychiatric disorders				
Anxiety				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Depression			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hallucination			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Blood creatinine increased			
subjects affected / exposed	3 / 112 (2.68%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Cervical vertebral fracture			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Procedural pneumothorax			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrioventricular block complete			
subjects affected / exposed	2 / 112 (1.79%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Atrioventricular block second degree			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			

subjects affected / exposed	2 / 112 (1.79%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiogenic shock			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Pericarditis			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Aphasia			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebral infarction			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular accident			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	2 / 112 (1.79%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 112 (1.79%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Agranulocytosis			

subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia				
subjects affected / exposed	2 / 112 (1.79%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Pancytopenia				
subjects affected / exposed	2 / 112 (1.79%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	1 / 1			
Thrombocytopenia				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Crohn`s disease				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	3 / 112 (2.68%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Diverticulum intestinal haemorrhagic				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dysphagia				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				

subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Large intestine perforation			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	2 / 112 (1.79%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Dermatosis			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	4 / 112 (3.57%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Hypothyroidism			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abscess soft tissue			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atypical pneumonia			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Clostridium difficile infection			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device related sepsis			
subjects affected / exposed	5 / 112 (4.46%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Enterococcal infection			
subjects affected / exposed	2 / 112 (1.79%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Erysipelas			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Escherichia bacteraemia			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Escherichia urinary tract infection			

subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Groin abscess				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peritonitis				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	15 / 112 (13.39%)			
occurrences causally related to treatment / all	3 / 16			
deaths causally related to treatment / all	1 / 5			
Pneumonia adenoviral				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia parainfluenzae viral				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary sepsis				
subjects affected / exposed	5 / 112 (4.46%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 2			
Sepsis				

subjects affected / exposed	10 / 112 (8.93%)			
occurrences causally related to treatment / all	4 / 10			
deaths causally related to treatment / all	0 / 3			
Septic shock				
subjects affected / exposed	7 / 112 (6.25%)			
occurrences causally related to treatment / all	3 / 7			
deaths causally related to treatment / all	1 / 2			
Staphylococcal infection				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Streptococcal sepsis				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Subcutaneous abscess				
subjects affected / exposed	2 / 112 (1.79%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Tonsillitis				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	3 / 112 (2.68%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 1			
Metabolism and nutrition disorders				
Dehydration				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diabetic metabolic decompensation				

subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	112 / 112 (100.00%)		
Vascular disorders			
Haematoma			
subjects affected / exposed	11 / 112 (9.82%)		
occurrences (all)	17		
Hypertension			
subjects affected / exposed	20 / 112 (17.86%)		
occurrences (all)	25		
Hypotension			
subjects affected / exposed	13 / 112 (11.61%)		
occurrences (all)	17		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	10 / 112 (8.93%)		
occurrences (all)	14		
Chest pain			
subjects affected / exposed	8 / 112 (7.14%)		
occurrences (all)	9		
Fatigue			
subjects affected / exposed	13 / 112 (11.61%)		
occurrences (all)	23		
Oedema			
subjects affected / exposed	6 / 112 (5.36%)		
occurrences (all)	6		
Oedema peripheral			
subjects affected / exposed	25 / 112 (22.32%)		
occurrences (all)	45		

Pain			
subjects affected / exposed	11 / 112 (9.82%)		
occurrences (all)	12		
Pyrexia			
subjects affected / exposed	95 / 112 (84.82%)		
occurrences (all)	162		
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	8 / 112 (7.14%)		
occurrences (all)	9		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	22 / 112 (19.64%)		
occurrences (all)	29		
Dyspnoea			
subjects affected / exposed	52 / 112 (46.43%)		
occurrences (all)	85		
Epistaxis			
subjects affected / exposed	15 / 112 (13.39%)		
occurrences (all)	16		
Pleural effusion			
subjects affected / exposed	15 / 112 (13.39%)		
occurrences (all)	18		
Respiratory failure			
subjects affected / exposed	8 / 112 (7.14%)		
occurrences (all)	9		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	6 / 112 (5.36%)		
occurrences (all)	7		
Sleep disorder			
subjects affected / exposed	22 / 112 (19.64%)		
occurrences (all)	34		
Investigations			
Alanine aminotransferase increased			

subjects affected / exposed	64 / 112 (57.14%)		
occurrences (all)	177		
Aspartate aminotransferase increased			
subjects affected / exposed	67 / 112 (59.82%)		
occurrences (all)	153		
Blood alkaline phosphatase increased	Additional description: Investigations		
subjects affected / exposed	58 / 112 (51.79%)		
occurrences (all)	164		
Blood bilirubin increased			
subjects affected / exposed	66 / 112 (58.93%)		
occurrences (all)	113		
Blood creatinine increased			
subjects affected / exposed	78 / 112 (69.64%)		
occurrences (all)	309		
C-reactive protein increased			
subjects affected / exposed	6 / 112 (5.36%)		
occurrences (all)	9		
Weight decreased			
subjects affected / exposed	61 / 112 (54.46%)		
occurrences (all)	162		
Weight increased			
subjects affected / exposed	26 / 112 (23.21%)		
occurrences (all)	48		
Injury, poisoning and procedural complications			
Allergic transfusion reaction			
subjects affected / exposed	10 / 112 (8.93%)		
occurrences (all)	11		
Fall			
subjects affected / exposed	7 / 112 (6.25%)		
occurrences (all)	8		
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	31 / 112 (27.68%)		
occurrences (all)	42		
Tachycardia			

subjects affected / exposed occurrences (all)	10 / 112 (8.93%) 13		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	 16 / 112 (14.29%) 20 29 / 112 (25.89%) 35 9 / 112 (8.04%) 11		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Leukopenia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all)	 13 / 112 (11.61%) 47 11 / 112 (9.82%) 50 7 / 112 (6.25%) 10 12 / 112 (10.71%) 48		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Diarrhoea	 13 / 112 (11.61%) 13 7 / 112 (6.25%) 8 67 / 112 (59.82%) 114		

subjects affected / exposed occurrences (all) Enteritis subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	55 / 112 (49.11%) 77 16 / 112 (14.29%) 18 66 / 112 (58.93%) 132 42 / 112 (37.50%) 71		
Skin and subcutaneous tissue disorders Dermatitis subjects affected / exposed occurrences (all) Petechiae subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	 28 / 112 (25.00%) 38 16 / 112 (14.29%) 18 6 / 112 (5.36%) 7 12 / 112 (10.71%) 13		
Renal and urinary disorders Acute kidney injury subjects affected / exposed occurrences (all) Haematuria subjects affected / exposed occurrences (all)	 22 / 112 (19.64%) 43 12 / 112 (10.71%) 16		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain	 6 / 112 (5.36%) 9		

subjects affected / exposed	17 / 112 (15.18%)		
occurrences (all)	22		
Musculoskeletal pain			
subjects affected / exposed	18 / 112 (16.07%)		
occurrences (all)	26		
Pain in extremity			
subjects affected / exposed	10 / 112 (8.93%)		
occurrences (all)	14		
Infections and infestations			
Clostridium difficile infection			
subjects affected / exposed	8 / 112 (7.14%)		
occurrences (all)	9		
Conjunctivitis			
subjects affected / exposed	7 / 112 (6.25%)		
occurrences (all)	8		
Device related infection			
subjects affected / exposed	19 / 112 (16.96%)		
occurrences (all)	24		
Enterococcal infection			
subjects affected / exposed	12 / 112 (10.71%)		
occurrences (all)	15		
Infection			
subjects affected / exposed	13 / 112 (11.61%)		
occurrences (all)	13		
Nasopharyngitis			
subjects affected / exposed	6 / 112 (5.36%)		
occurrences (all)	7		
Oral herpes			
subjects affected / exposed	17 / 112 (15.18%)		
occurrences (all)	22		
Pneumonia	Additional description: Infections and infestations		
subjects affected / exposed	38 / 112 (33.93%)		
occurrences (all)	53		
Pneumonia fungal			
subjects affected / exposed	15 / 112 (13.39%)		
occurrences (all)	23		

Respiratory tract infection subjects affected / exposed occurrences (all)	7 / 112 (6.25%) 8		
Sepsis subjects affected / exposed occurrences (all)	9 / 112 (8.04%) 10		
Septic shock subjects affected / exposed occurrences (all)	7 / 112 (6.25%) 7		
Sinusitis subjects affected / exposed occurrences (all)	6 / 112 (5.36%) 8		
Soft tissue infection subjects affected / exposed occurrences (all)	16 / 112 (14.29%) 19		
Staphylococcal infection subjects affected / exposed occurrences (all)	22 / 112 (19.64%) 29		
Urinary tract infection subjects affected / exposed occurrences (all)	12 / 112 (10.71%) 15		
Urosepsis subjects affected / exposed occurrences (all)	6 / 112 (5.36%) 6		
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	11 / 112 (9.82%) 12		
Hyperkalaemia subjects affected / exposed occurrences (all)	6 / 112 (5.36%) 10		
Hypokalaemia subjects affected / exposed occurrences (all)	23 / 112 (20.54%) 31		
Hypoproteinaemia			

subjects affected / exposed occurrences (all)	88 / 112 (78.57%) 221		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 May 2017	- update of the expected duration of trial, because the start of the study was delayed for organizational reasons and the three interim analyses stopped recruitment and thus the involvement of further clinical centers was delayed. - secondary endpoint: Days alive and out of hospital: no further documentation of hospitalization after the end of study treatment, because the hospitalization not performed study-related - update of the site effects of Azacitidine - IWG criteria were supplemented by the criterion "stable disease" to assess the response during therapy with Azacitidine - correction of spelling mistakes

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported