



Clinical trial results:

An Investigator-Initiated Study To Evaluate Ara-C and Idarubicin in Combination with the Selective Inhibitor Of Nuclear Export (SINE) Selinexor (KPT-330) in Patients with Relapsed Or Refractory AML

Summary

EudraCT number	2014-000526-37
Trial protocol	DE
Global end of trial date	31 July 2018

Results information

Result version number	v1 (current)
This version publication date	04 February 2022
First version publication date	04 February 2022
Summary attachment (see zip file)	SAIL CSR Synopsis (SAIL CSR Final v1.0 20190731_synopsis.pdf)

Trial information

Trial identification

Sponsor protocol code	SAIL
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02249091
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GSO Global Clinical Research B.V.
Sponsor organisation address	Keizersgracht 62-64, Amsterdam, Netherlands, 1015
Public contact	Projectmanagement, GSO Global Clinical Research B.V., +49 4044195460, kranich@gsoglobal.com
Scientific contact	Projectmanagement, GSO Global Clinical Research B.V., +49 4044195460, kranich@gsoglobal.com

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	31 July 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 August 2017
Global end of trial reached?	Yes
Global end of trial date	31 July 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the efficacy of Selinexor in combination with standard chemotherapy in patients with relapsed/ refractory AML by determination of rate of complete remission (CR) or morphologic complete remission with incomplete blood count recovery (CRi), as defined by the recommendations on diagnosis and management of AML in adults from an international expert panel, on behalf of the European LeukemiaNet

Protection of trial subjects:

The study was conducted in compliance with Good Clinical Practice (GCP) and the Declaration of Helsinki, and in accordance with applicable local and regulatory requirements. Patients were closely monitored for adverse events (AEs) during treatment and AEs were captured up to 30 days after the last dose of study medication. The majority of side effects of selinexor were known to be related to low grade nausea and reversible anorexia with weight loss. Fatigue was also observed, and this might be related to reduced caloric (and fluid) intake. These adverse effects were reduced or eliminated with prophylactic appetite stimulants (megestrol and olanzapin or mirtazapine) and prophylactic anti-emesis (ondansetron or similar 5-HT3 antagonist). Platelet count reductions, primarily in patients with baseline thrombocytopenia, were observed, but manageable with dose modification, interruption, platelet transfusions, and/or platelet stimulator support. Diverse ocular symptoms, primarily blurred vision, have been reported and ophthalmologic examinations were part of protocol assessments. The protocol gave detailed guidance for interruption and dose reduction of study medication for the most frequently observed adverse effects. As acetaminophen can interfere with the metabolism of selinexor patients were advised to minimize the use of products containing acetaminophen. Common side effects of induction therapy with Ara-C and idarubicin are bone marrow suppression. Due to low blood counts the risk for infection was increased. Patients were hospitalized as required during induction therapy to closely monitor their safety parameters and received corresponding treatment, if applicable.

Background therapy:

Background chemotherapy consisted of cytarabine (cytosine arabinoside/Ara-C) and idarubicin according to the 7+3 schedule.

All enrolled patients were treated with cytarabine at a dose of 100 mg/m² continuous infusion (day 1-7) and idarubicin at a dose of 10 mg/m² i.v. (days 1,3,5) every 4 weeks for a maximum of 2 cycles. During the second cycle the idarubicin dose was restricted to 2 administrations on day 1 and 3.

If after 1 or 2 induction cycles patients were not eligible for or did not undergo stem cell transplantation, 3 cycles of consolidation therapy with Selinexor and cytarabine could be applied until relapse or toxicity developed. The dose of cytarabine was 3 g/m² i.v. for 2h every 12 hours at 3 consecutive days for patients with good performance status and younger than 60 years (in total 6 doses). For patients older than 60 years the dose was 1 g/m² i.v. for 2h every 12 hours at 3 consecutive days.

Evidence for comparator: -

Actual start date of recruitment	15 July 2014
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: 42
Worldwide total number of subjects	42
EEA total number of subjects	42

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)	26
From 65 to 84 years	16
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between September 2014 and June 2016 a total of 43 patients were registered in the clinical trial at 3 sites in Germany. One patient was a screening failure. Of the remaining 42 patients, the first 27 patients were treated in cohort 1 and the other 15 patients were treated in cohort 2.

Pre-assignment

Screening details:

Patients with cytological or histological diagnosis of AML were recruited from the patient pool of the participating study sites. Patients had to have relapsed/refractory disease, relapse after stem cell transplantation was permitted.

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	Cohort 1

Arm description:

Selinexor was administered at a dose of 40 mg/m² twice weekly orally starting on day 2 of a 4-week induction cycle (Monday/Wednesday or Tuesday/Thursday or Wednesday/Friday) with a total of 8 doses per induction cycle. Background chemotherapy consisted of cytarabine and idarubicin according to 7+3 schedule. A maximum of 2 induction cycles was given.

After the induction cycles patients not undergoing stem cell transplantation and benefitting from Selinexor could receive 3x4 weeks of consolidation therapy or Selinexor maintenance therapy for a maximum of 1 year or until relapse. The Selinexor schedule remained the same as during the induction therapy.

Arm type	Experimental
Investigational medicinal product name	Selinexor
Investigational medicinal product code	KPT-330
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

40 mg/m² twice weekly orally starting on day 2 of a 4-week induction cycle (Monday/Wednesday or Tuesday/Thursday or Wednesday/Friday) with a total of 8 doses per induction cycle for 1 or 2 induction cycles plus 3 4-weeks cycles (if applicable) plus maintenance until relapse or a maximum of 1 year after start of treatment.

Arm title	Cohort 2
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Arm description:

Selinexor was administered at a flat dose of 60 mg twice weekly orally during weeks 1-3 of a 4-week cycle (day 2, 4, 9, 11, 16, 18) starting on day 2 (Monday/Wednesday or Tuesday/Thursday or Wednesday/Friday) with a total of 6 doses per induction cycle. Background chemotherapy consisted of cytarabine and idarubicin according to 7+3 schedule. A maximum of 2 induction cycles was given. After the induction cycles patients not undergoing stem cell transplantation and benefitting from Selinexor could receive 3x4 weeks of consolidation therapy or Selinexor maintenance therapy for a maximum of 1 year or until relapse. The Selinexor schedule remained the same as during the induction therapy.

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Number of subjects in period 1	Cohort 1	Cohort 2
Started	27	15
Completed	7	2
Not completed	20	13
Adverse event, serious fatal	3	4
Consent withdrawn by subject	2	2
Physician decision	4	1
CR with subsequent donor lymphocyte infusion	1	-
Adverse event, non-fatal	1	-
Stable disease with following SCT	-	1
Refractory AML	1	1
Ongoing bone marrow aplasia, periph. pancytopenia	-	1
Lack of efficacy	8	3

Baseline characteristics

Reporting groups

Reporting group title	Cohort 1
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Reporting group description:

Selinexor was administered at a dose of 40 mg/m² twice weekly orally starting on day 2 of a 4-week induction cycle (Monday/Wednesday or Tuesday/Thursday or Wednesday/Friday) with a total of 8 doses per induction cycle. Background chemotherapy consisted of cytarabine and idarubicin according to 7+3 schedule. A maximum of 2 induction cycles was given.

After the induction cycles patients not undergoing stem cell transplantation and benefitting from Selinexor could receive 3x4 weeks of consolidation therapy or Selinexor maintenance therapy for a maximum of 1 year or until relapse. The Selinexor schedule remained the same as during the induction therapy.

Reporting group title	Cohort 2
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Reporting group description:

Selinexor was administered at a flat dose of 60 mg twice weekly orally during weeks 1-3 of a 4-week cycle (day 2, 4, 9, 11, 16, 18) starting on day 2 (Monday/Wednesday or Tuesday/Thursday or Wednesday/Friday) with a total of 6 doses per induction cycle. Background chemotherapy consisted of cytarabine and idarubicin according to 7+3 schedule. A maximum of 2 induction cycles was given. After the induction cycles patients not undergoing stem cell transplantation and benefitting from Selinexor could receive 3x4 weeks of consolidation therapy or Selinexor maintenance therapy for a maximum of 1 year or until relapse. The Selinexor schedule remained the same as during the induction therapy.

Reporting group values	Cohort 1	Cohort 2	Total
Number of subjects	27	15	42
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	58.0	60.0	
full range (min-max)	22 to 78	29 to 77	-
Gender categorical			
Units: Subjects			
Female	11	6	17
Male	16	9	25
Leukemia diagnosis			
Units: Subjects			
De-novo AML	19	12	31
Secondary AML	6	3	9
Therapy-induced AML	2	0	2
Prior stem cell transplantation (SCT)			
Units: Subjects			

Yes	10	7	17
No	17	8	25
Duration of remission prior SAIL			
Units: Subjects			
<12 months	9	4	13
>12 months	11	7	18
Refractory disease	7	4	11

Subject analysis sets

Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:

The full analysis set included all 42 patients who had received at least one dose of study medication and for whom post-baseline efficacy data were available.

Reporting group values	Full Analysis Set		
Number of subjects	42		
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	59.5		
full range (min-max)	22 to 78		
Gender categorical			
Units: Subjects			
Female	17		
Male	25		
Leukemia diagnosis			
Units: Subjects			
De-novo AML	31		
Secondary AML	9		
Therapy-induced AML	2		
Prior stem cell transplantation (SCT)			
Units: Subjects			
Yes	17		
No	25		
Duration of remission prior SAIL			
Units: Subjects			
<12 months	13		
>12 months	18		

Refractory disease	11		
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End points

End points reporting groups

Reporting group title	Cohort 1
Reporting group description: Selinexor was administered at a dose of 40 mg/m ² twice weekly orally starting on day 2 of a 4-week induction cycle (Monday/Wednesday or Tuesday/Thursday or Wednesday/Friday) with a total of 8 doses per induction cycle. Background chemotherapy consisted of cytarabine and idarubicin according to 7+3 schedule. A maximum of 2 induction cycles was given. After the induction cycles patients not undergoing stem cell transplantation and benefitting from Selinexor could receive 3x4 weeks of consolidation therapy or Selinexor maintenance therapy for a maximum of 1 year or until relapse. The Selinexor schedule remained the same as during the induction therapy.	
Reporting group title	Cohort 2
Reporting group description: Selinexor was administered at a flat dose of 60 mg twice weekly orally during weeks 1-3 of a 4-week cycle (day 2, 4, 9, 11, 16, 18) starting on day 2 (Monday/Wednesday or Tuesday/Thursday or Wednesday/Friday) with a total of 6 doses per induction cycle. Background chemotherapy consisted of cytarabine and idarubicin according to 7+3 schedule. A maximum of 2 induction cycles was given. After the induction cycles patients not undergoing stem cell transplantation and benefitting from Selinexor could receive 3x4 weeks of consolidation therapy or Selinexor maintenance therapy for a maximum of 1 year or until relapse. The Selinexor schedule remained the same as during the induction therapy.	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description: The full analysis set included all 42 patients who had received at least one dose of study medication and for whom post-baseline efficacy data were available.	

Primary: Number of subjects with CR/CRi = Overall Response Rate

End point title	Number of subjects with CR/CRi = Overall Response Rate
End point description: Efficacy of selinexor in combination with standard chemotherapy in patients with relapsed/refractory AML by determination of rate of complete response (CR) or morphologic CR with incomplete blood count recovery (CRi), as defined by the recommendations on diagnosis and management of AML in adults from an international expert panel, on behalf of the European LeukemiaNet: CR: Absolute Neutrophil count (ANC) >1.0x10^9/L, Platelet count >100x10^9/L, Bone marrow blasts <5%, no Auer rods, no evidence of extramedullary disease. CRi: Same as CR, but ANC may be <1.0x10^9/L and/or Platelet count <100x10^9/L. Patients with morphologic leukemia-free state (MLFS) were included in the group of responders. MLFS: Bone marrow blasts <5%, no Auer rods, no evidence of extramedullary disease. The best response after selinexor treatment was analyzed, thus the best response after induction cycle(s).	
End point type	Primary
End point timeframe: 1-2 induction cycles (4-8 weeks)	

End point values	Cohort 1	Cohort 2	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	27	15	42	
Units: Number of subjects				
Number of subjects with CR	6	3	9	
Number of subjects with CRi	9	2	11	
Number of subjects with MLFS	0	1	1	

Non-responder	12	9	21	
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Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Cohort 2 v Cohort 1 v Full Analysis Set
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0023
Method	Fisher exact
Parameter estimate	Wilson
Point estimate	50
Confidence interval	
level	95 %
sides	2-sided
lower limit	37.7
upper limit	62.3

Secondary: Number of subjects with partial remission (PR) = Rate of PR

End point title	Number of subjects with partial remission (PR) = Rate of PR
End point description:	
Efficacy of selinexor in combination with standard chemotherapy in patients with relapsed/refractory AML by determination of rate of partial remission (PR), as defined by the recommendations on diagnosis and management of AML in adults from an international expert panel, on behalf of the European LeukemiaNet:	
PR: Absolute Neutrophil count (ANC) >1.0x10 ⁹ /L, Platelet count > 100x10 ⁹ /L, at least a 50% decrease in the percentage of bone marrow aspirate blasts to 5-25%, or bone marrow blasts <5% with persistent Auer rods.	
The best response after selinexor treatment was analyzed, thus the best response after the induction cycle(s).	
End point type	Secondary
End point timeframe:	
1-2 induction cycles (4-8 weeks)	

End point values	Cohort 1	Cohort 2	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	27	15	42	
Units: subjects				
Number of subjects with PR	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects transplanted after induction therapy (Stem Cell Transplantation)

End point title	Number of subjects transplanted after induction therapy (Stem Cell Transplantation)
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End point description:

End point type	Secondary
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End point timeframe:

1-2 induction cycles (4-8 weeks)

End point values	Cohort 1	Cohort 2	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	27	15	42	
Units: subjects				
SCT applied	11	4	15	
SCT not applied	16	11	27	

Statistical analyses

No statistical analyses for this end point

Secondary: Early death rate

End point title	Early death rate
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End point description:

Early death was defined as death before the end of the first induction cycle.

End point type	Secondary
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End point timeframe:

One induction cycle (4 weeks)

End point values	Cohort 1	Cohort 2	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	27	15	42	
Units: subjects				
Number of subjects with early death	0	4	4	

Statistical analyses

No statistical analyses for this end point

Secondary: Event-Free Survival

End point title	Event-Free Survival
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End point description:

Event-free survival (EFS) was calculated from the time of informed consent until death, not achieving CR/CRi or relapse after CR/CRi.

End point type	Secondary
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End point timeframe:

Time from registration to event, max. 2 years.

End point values	Cohort 1	Cohort 2	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	27	15	42	
Units: months				
median (confidence interval 95%)				
Event-free survival	5.6 (2.9 to 12.6)	4.3 (0.9 to 10.4)	4.9 (3.0 to 8.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival

End point title	Progression-free survival
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End point description:

Progression-free survival (PFS) was calculated from the time of informed consent to the date of recurrence or death, whichever occurred first. Subjects were censored at the date of the last follow-up visit if they were alive without relapse.

Disease progression was defined as presence of >50% increase in bone marrow blasts to a level of at least 50% and/or a doubling of the percentage of peripheral blood blasts to a level of at least 50%.

End point type	Secondary
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End point timeframe:

Time from registration to event, max. 2 years.

End point values	Cohort 1	Cohort 2	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	27	15	42	
Units: months				
median (confidence interval 95%)				
Progression-free survival	6.3 (2.3 to 26.3)	4.3 (0.9 to 12.9)	6.1 (2.3 to 12.9)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Throughout the treatment period from start of treatment until one month after the last dose of study medication, on average 2 months.

Adverse event reporting additional description:

AEs could be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. In order to prevent reporting bias, investigators were advised not to question subjects regarding specific occurrence of one or more AEs. AEs were requested to be captured at each patient visit.

Assessment type	Systematic
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Dictionary used

Dictionary name	NCI-CTCAE
Dictionary version	4.03

Reporting groups

Reporting group title	Cohort 1
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Reporting group description:

Selinexor was administered at a dose of 40 mg/m² twice weekly orally starting on day 2 of a 4-week induction cycle (Monday/Wednesday or Tuesday/Thursday or Wednesday/Friday) with a total of 8 doses per induction cycle. Background chemotherapy consisted of cytarabine and idarubicine according to 7+3 schedule. A maximum of 2 induction cycles was given.

After the induction cycles patients not undergoing stem cell transplantation and benefitting from Selinexor could receive 3x4 weeks of consolidation therapy or Selinexor maintenance therapy for a maximum of 1 year or until relapse. The Selinexor schedule remained the same as during the induction therapy.

Reporting group title	Cohort 2
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Reporting group description:

Selinexor was administered at a flat dose of 60 mg twice weekly orally during weeks 1-3 of a 4-week cycle (day 2, 4, 9, 11, 16, 18) starting on day 2 (Monday/Wednesday or Tuesday/Thursday or Wednesday/Friday) with a total of 6 doses per induction cycle. Background chemotherapy consisted of cytarabine and idarubicine according to 7+3 schedule. A maximum of 2 induction cycles was given. After the induction cycles patients not undergoing stem cell transplantation and benefitting from Selinexor could receive 3x4 weeks of consolidation therapy or Selinexor maintenance therapy for a maximum of 1 year or until relapse. The Selinexor schedule remained the same as during the induction therapy.

Serious adverse events	Cohort 1	Cohort 2	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 27 (44.44%)	8 / 15 (53.33%)	
number of deaths (all causes)	16	9	
number of deaths resulting from adverse events	7	6	
Investigations			
Blood bilirubin increased			
subjects affected / exposed	1 / 27 (3.70%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased	Additional description: Neutropenia		

subjects affected / exposed	0 / 27 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fracture			
subjects affected / exposed	1 / 27 (3.70%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 27 (3.70%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Asystole			
subjects affected / exposed	0 / 27 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Atrial fibrillation			
subjects affected / exposed	1 / 27 (3.70%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Stroke	Additional description: Multiple brain infarctions		
subjects affected / exposed	1 / 27 (3.70%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Subarachnoidal hemorrhage			
subjects affected / exposed	1 / 27 (3.70%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Blood and lymphatic system disorders			
Anemia			

subjects affected / exposed	0 / 27 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow hypocellular	Additional description: Bone marrow aplasia		
subjects affected / exposed	0 / 27 (0.00%)	2 / 15 (13.33%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 27 (3.70%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fever			
subjects affected / exposed	1 / 27 (3.70%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General weakness			
subjects affected / exposed	1 / 27 (3.70%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SIRS	Additional description: Systemic inflammatory response syndrom		
subjects affected / exposed	1 / 27 (3.70%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Immune system disorders			
GvHD	Additional description: Graft-versus-host-disease		
subjects affected / exposed	1 / 27 (3.70%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemophagocytosis syndrome	Additional description: Lymphohistiocytic syndrome; cause of patient's death according to autopsy report: hemophagocytosis syndrome with acute cardiac decompensation		
subjects affected / exposed	0 / 27 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	

Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 27 (3.70%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 27 (3.70%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Septic shock			
subjects affected / exposed	1 / 27 (3.70%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
	Additional description: Pneumonia		
subjects affected / exposed	3 / 27 (11.11%)	2 / 15 (13.33%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Sepsis			
subjects affected / exposed	1 / 27 (3.70%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

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

Non-serious adverse events	Cohort 1	Cohort 2	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 27 (100.00%)	15 / 15 (100.00%)	
Vascular disorders			
Haematoma			
subjects affected / exposed	5 / 27 (18.52%)	2 / 15 (13.33%)	
occurrences (all)	7	3	
Hypertension			
subjects affected / exposed	2 / 27 (7.41%)	3 / 15 (20.00%)	
occurrences (all)	2	3	

Hypotension subjects affected / exposed occurrences (all)	12 / 27 (44.44%) 16	7 / 15 (46.67%) 7	
General disorders and administration site conditions			
Injection site reaction subjects affected / exposed occurrences (all)	10 / 27 (37.04%) 12	3 / 15 (20.00%) 5	
Edema face subjects affected / exposed occurrences (all)	3 / 27 (11.11%) 3	0 / 15 (0.00%) 0	
Edema limbs subjects affected / exposed occurrences (all)	6 / 27 (22.22%) 8	5 / 15 (33.33%) 6	
Fatigue subjects affected / exposed occurrences (all)	18 / 27 (66.67%) 23	9 / 15 (60.00%) 15	
Fever subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2	5 / 15 (33.33%) 9	
Immune system disorders			
Allergic reaction subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 3	2 / 15 (13.33%) 2	
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	2 / 15 (13.33%) 2	
Dyspnoea subjects affected / exposed occurrences (all)	5 / 27 (18.52%) 5	2 / 15 (13.33%) 2	
Epistaxis subjects affected / exposed occurrences (all)	10 / 27 (37.04%) 13	8 / 15 (53.33%) 13	
Pleural effusion subjects affected / exposed occurrences (all)	3 / 27 (11.11%) 3	1 / 15 (6.67%) 1	

Psychiatric disorders			
Depression			
subjects affected / exposed	5 / 27 (18.52%)	3 / 15 (20.00%)	
occurrences (all)	5	3	
Insomnia			
subjects affected / exposed	5 / 27 (18.52%)	2 / 15 (13.33%)	
occurrences (all)	6	2	
Investigations			
Creatinine increased			
subjects affected / exposed	3 / 27 (11.11%)	2 / 15 (13.33%)	
occurrences (all)	3	2	
Neutrophil count decreased			
subjects affected / exposed	12 / 27 (44.44%)	6 / 15 (40.00%)	
occurrences (all)	14	15	
Platelet count decreased			
subjects affected / exposed	19 / 27 (70.37%)	7 / 15 (46.67%)	
occurrences (all)	33	23	
Weight gain			
subjects affected / exposed	2 / 27 (7.41%)	1 / 15 (6.67%)	
occurrences (all)	2	1	
White blood cell decreased			
subjects affected / exposed	17 / 27 (62.96%)	9 / 15 (60.00%)	
occurrences (all)	21	23	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	4 / 27 (14.81%)	1 / 15 (6.67%)	
occurrences (all)	6	1	
Cardiac disorders			
Left ventricular systolic dysfunction			
subjects affected / exposed	2 / 27 (7.41%)	1 / 15 (6.67%)	
occurrences (all)	2	1	
Sinus tachycardia			
subjects affected / exposed	3 / 27 (11.11%)	3 / 15 (20.00%)	
occurrences (all)	3	4	
Nervous system disorders			

Dizziness subjects affected / exposed occurrences (all)	9 / 27 (33.33%) 12	6 / 15 (40.00%) 6	
Dysgeusia subjects affected / exposed occurrences (all)	3 / 27 (11.11%) 3	0 / 15 (0.00%) 0	
Headache subjects affected / exposed occurrences (all)	5 / 27 (18.52%) 10	3 / 15 (20.00%) 4	
Presyncope subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2	1 / 15 (6.67%) 1	
Syncope subjects affected / exposed occurrences (all)	5 / 27 (18.52%) 5	1 / 15 (6.67%) 1	
Blood and lymphatic system disorders Anemia subjects affected / exposed occurrences (all)	20 / 27 (74.07%) 33	5 / 15 (33.33%) 27	
Febrile neutropenia subjects affected / exposed occurrences (all)	23 / 27 (85.19%) 30	5 / 15 (33.33%) 27	
Ear and labyrinth disorders Hearing impaired subjects affected / exposed occurrences (all)	3 / 27 (11.11%) 4	1 / 15 (6.67%) 1	
Vertigo subjects affected / exposed occurrences (all)	4 / 27 (14.81%) 4	0 / 15 (0.00%) 0	
Eye disorders Blurred vision subjects affected / exposed occurrences (all)	3 / 27 (11.11%) 3	0 / 15 (0.00%) 0	
Dry eye subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2	1 / 15 (6.67%) 1	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	10 / 27 (37.04%)	1 / 15 (6.67%)	
occurrences (all)	10	1	
Colitis			
subjects affected / exposed	3 / 27 (11.11%)	0 / 15 (0.00%)	
occurrences (all)	3	0	
Constipation			
subjects affected / exposed	7 / 27 (25.93%)	7 / 15 (46.67%)	
occurrences (all)	8	10	
Diarrhoea			
subjects affected / exposed	24 / 27 (88.89%)	11 / 15 (73.33%)	
occurrences (all)	99	32	
Dysphagia			
subjects affected / exposed	2 / 27 (7.41%)	1 / 15 (6.67%)	
occurrences (all)	2	1	
Mucositis oral			
subjects affected / exposed	12 / 27 (44.44%)	6 / 15 (40.00%)	
occurrences (all)	19	7	
Nausea			
subjects affected / exposed	23 / 27 (85.19%)	13 / 15 (86.67%)	
occurrences (all)	49	19	
Oral haemorrhage			
subjects affected / exposed	3 / 27 (11.11%)	0 / 15 (0.00%)	
occurrences (all)	4	0	
Stomach pain			
subjects affected / exposed	3 / 27 (11.11%)	1 / 15 (6.67%)	
occurrences (all)	3	1	
Toothache			
subjects affected / exposed	4 / 27 (14.81%)	0 / 15 (0.00%)	
occurrences (all)	5	0	
Vomiting			
subjects affected / exposed	22 / 27 (81.48%)	9 / 15 (60.00%)	
occurrences (all)	46	13	
Skin and subcutaneous tissue disorders			
Alopecia			

subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2	1 / 15 (6.67%) 1	
Rash maculo-papular subjects affected / exposed occurrences (all)	4 / 27 (14.81%) 6	1 / 15 (6.67%) 1	
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	3 / 15 (20.00%) 3	
Urinary incontinence subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2	1 / 15 (6.67%) 1	
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2	1 / 15 (6.67%) 2	
Chest wall pain subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2	1 / 15 (6.67%) 1	
Pain in extremity subjects affected / exposed occurrences (all)	3 / 27 (11.11%) 3	1 / 15 (6.67%) 1	
Infections and infestations Catheter related infection subjects affected / exposed occurrences (all)	4 / 27 (14.81%) 4	1 / 15 (6.67%) 1	
Lung infection subjects affected / exposed occurrences (all)	8 / 27 (29.63%) 13	4 / 15 (26.67%) 15	
Sepsis subjects affected / exposed occurrences (all)	7 / 27 (25.93%) 7	3 / 15 (20.00%) 4	
Sinusitis subjects affected / exposed occurrences (all)	3 / 27 (11.11%) 4	0 / 15 (0.00%) 0	
Metabolism and nutrition disorders			

Anorexia			
subjects affected / exposed	22 / 27 (81.48%)	8 / 15 (53.33%)	
occurrences (all)	40	10	
Hyperglycaemia			
subjects affected / exposed	4 / 27 (14.81%)	1 / 15 (6.67%)	
occurrences (all)	4	2	
Hypocalcaemia			
subjects affected / exposed	4 / 27 (14.81%)	1 / 15 (6.67%)	
occurrences (all)	5	1	
Hypokalaemia			
subjects affected / exposed	17 / 27 (62.96%)	2 / 15 (13.33%)	
occurrences (all)	27	2	
Hypomagnesaemia			
subjects affected / exposed	3 / 27 (11.11%)	1 / 15 (6.67%)	
occurrences (all)	3	1	
Hyponatraemia			
subjects affected / exposed	3 / 27 (11.11%)	4 / 15 (26.67%)	
occurrences (all)	4	6	
Hypophosphataemia			
subjects affected / exposed	3 / 27 (11.11%)	0 / 15 (0.00%)	
occurrences (all)	4	0	
Weight loss			
subjects affected / exposed	2 / 27 (7.41%)	2 / 15 (13.33%)	
occurrences (all)	3	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 September 2014	Protocol v1.2 dd. Sep01, 2014: The full ophthalmologic examination at baseline and if clinically indicated during treatment has been implemented into the protocol as part of the safety assessments in order to help determine if selinexor is contributing any visual changes. In phase I clinical trials, a baseline full ophthalmologic examination had been implemented since November 2012, because there had been few reports of "blurred vision" and other visual changes during 2 phase I trials with selinexor.
24 August 2015	Protocol v2.0 dated Aug24, 2015: The findings of the study showed that very good response was achieved with treatment with Ara-C and idarubicin in combination with selinexor. The most frequent non-haematologic AEs observed had included vomiting, diarrhoea, nausea, fatigue, anorexia and neutropenic fever. Taking into account the promising results, 15 more subjects were planned to be recruited reaching a total of approximately 40 subjects for the trial. The sample size calculation, statistical considerations, the anticipated enrolment period, and the planned duration of the study had been updated accordingly. The new cohort of subjects was to receive selinexor at a flat dose of 60 mg twice weekly in weeks 1-3 of a 4-week cycle. The objective of the new dose regimen was to improve management of most common AEs and further investigate the response to treatment. Dose modification levels had been adapted accordingly. Furthermore, several sections in the protocol related to treatment, dose modification, concomitant medication, and supportive care guidelines were updated according to the updated Investigator's Brochure v5.0 dated Aug12, 2015.
13 January 2017	Protocol v3.1 dated Jan13, 2017: The protocol was updated following the regular update of the Reference Safety Information (Investigator's Brochure Selinexor). Also finishing Source Data Verification and collecting data for final study results revealed the necessity of additional data to interpret the safety and efficacy. Additional data (time to platelet recovery to platelets $\geq 50 \times 10^9/L$ and $\geq 100 \times 10^9/L$ and time to Absolute neutrophil count (ANC) recovery to ANC $\geq 0.5 \times 10^9/L$ and $\geq 1.0 \times 10^9/L$) were to be collected to define the recovery times for platelets and neutrophils in more detail. The primary objective "remission status after induction" was to be classified according to Doehner et al.: the recommendations from the European LeukemiaNet (Blood. 2004 Jan 15;103(2):479-85), and not according to Cheson et al. An Independent Data Monitoring Committee consisting of 2-3 AML specialists was implemented to make recommendations regarding the interpretation of the safety and efficacy results. The protocol was updated accordingly to the Investigator's Brochure (IB) v6.0 dated Nov14, 2016. Subsequently to the IB update, all cases of cerebellar toxicity \geq Grade 3 were added as Adverse Events of Special Interest and were to be reported in the same format and timeframe as Serious Adverse Events. An addendum to subject's information (v3.0 dated Dec14, 2016) for subjects still in maintenance therapy and follow-up had been updated in accordance with the amended protocol and IB.

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/32515072>