Clinical trial results:
An Open-Label, Multicenter Study of the Effects of Remission Maintenance Therapy with Ceplene® (Histamine Dihydrochloride), Given in Conjunction with Low-Dose Interleukin-2 (IL-2, Proleukin®), on Immune Response and Minimal Residual Disease (MRD) in Adult Patients with Acute Myeloid Leukemia (AML) in First Complete Remission (CR1)

Summary

EudraCT number	2009-012083-14
Trial protocol	SE BE GB ES IT FR
Global end of trial date	04 June 2014

Results information

Result version number	v1
This version publication date	28 April 2016
First version publication date	28 April 2016

Trial information

Trial identification

Sponsor protocol code	EPC2008-02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01347996
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	MEDA Pharma GmbH & Co. KG
Sponsor organisation address	Benzstrasse 1, Bad Homburg, Germany, 61352
Public contact	Group leader study manager, MEDA Pharma GmbH & Co. KG, +49 6172 888 01, 42b@medapharma.de
Scientific contact	Head of Corporate Clinical Affairs, MEDA Pharma GmbH & Co. KG, +49 6172 888 01, 42b@medapharma.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	15 October 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 June 2014
Global end of trial reached?	Yes
Global end of trial date	04 June 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

1. The quantitative and qualitative pharmacodynamic effects of Ceplene plus low dose IL-2 (Ceplene/IL-2) by monitoring T and NK cell phenotypes and their functionality after the first and third cycles of treatment in adult patients with acute myeloid leukemia (AML) in first complete remission (CR1).

2. Minimal residual disease (MRD) in AML patients receiving Ceplene/IL-2.

Protection of trial subjects:

Patients were withdrawn from study treatment:
• in case of relapse of AML;
• in case of unmanageable or irreversible toxicity using the CTCAE v3.0 criteria as de-fined in Appendix 2 of the study protocol. Patients with recurrent Grade 3 or 4 toxicity after dose reductions did no longer receive treatment, but must be followed for up to 2 years for relapse, or death, whichever comes first;
• if, in the opinion of the Investigator, it was not in the patient's best interest to continue (e.g., adverse event, concurrent illness, etc.).
The patients could withdraw from treatment at any time and for any reason.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 September 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 41
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Belgium: 10
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	Italy: 19
Worldwide total number of subjects	84
EEA total number of subjects	84

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)	52
From 65 to 84 years	32
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

As AML is a rare disease belonging to the group of acute leukemias, which account for less than 3% of all cancers, it was necessary to conduct the study involving study sites across different European countries to assure patient recruitment in a reasonable time period.

Pre-assignment

Screening details:

Adult (≥18 years of age) AML patients in CR1 (defined as less than 5% blasts in a normocel-lular BM) who had been genetically well-characterized at diagnosis were considered for participation. Patients should have performed conventional cytogenetic AML subtyping and molecular characterization on diagnositic BM samples using RQ-PCR techniques.

Period 1

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

Arms

Arm title	Ceplene/IL-2

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Histamine dihydrochloride / Ceplene®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Ceplene was administered sc 0.5 mg bid after IL-2.

Investigational medicinal product name	Interleukin-2 / Proleukin®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

IL-2 was administered subcutaneously (sc), 1 µg/kg [16,400 IU/kg] body weight twice daily (bid) during treatment periods.

Number of subjects in period 1	Ceplene/IL-2
Started	84
Completed	33
Not completed	51
Consent withdrawn by subject	3
Relapse	37
Adverse event, non-fatal	9

Any other reasons	2

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	84	84	
Age categorical Units: Subjects			
<= 60 years	41	41	
> 60 years	43	43	
Age continuous Units: years			
arithmetic mean	58.08		
standard deviation	± 14.359	-	
Gender categorical Units: Subjects			
Female	44	44	
Male	40	40	

End points

End points reporting groups

Reporting group title	Ceplene/IL-2
Reporting group description: -	
Subject analysis set title	Samples with cell counts at day 1
Subject analysis set type	Full analysis
Subject analysis set description: The subjects with evaluable cell counts at Day 1.	
Subject analysis set title	Samples with cell counts at day 21
Subject analysis set type	Full analysis
Subject analysis set description: The subjects with evaluable cell counts at Day 21.	
Subject analysis set title	Samples at day 1 / subset of cells CD3+ CD4+
Subject analysis set type	Full analysis
Subject analysis set description: The subjects with evaluable biomarkers at Day 1, subset of cells CD3+ CD4+	
Subject analysis set title	Samples at day 21 / subset of cells CD3+ CD4+
Subject analysis set type	Full analysis
Subject analysis set description: The subjects with available biomarkers at day 21 of cycle 1, subset of cells CD3+ CD4+	
Subject analysis set title	Samples at day 1 / subset of cells CD3+ CD8+
Subject analysis set type	Full analysis
Subject analysis set description: The subjects with evaluable biomarkers at Day 1, subset of cells CD3+ CD8+	
Subject analysis set title	Samples at day 21 / subset of cells CD3+ CD8+
Subject analysis set type	Full analysis
Subject analysis set description: The subjects with evaluable biomarkers at Day 21, subset of cells CD3+ CD8+	
Subject analysis set title	Samples at day 1 / subset of cells CD3- CD56+ dim CD16+
Subject analysis set type	Full analysis
Subject analysis set description: The subjects with evaluable biomarkers at Day 1, subset of cells CD3- CD56+ dim CD16+	
Subject analysis set title	Samples at day 21 / subset of cells CD3- CD56+ dim CD16+
Subject analysis set type	Full analysis
Subject analysis set description: The subjects with evaluable biomarkers at Day 21, subset of cells CD3- CD56+ dim CD16+	
Subject analysis set title	Samples at day 1 / subset of cells CD3- CD56+
Subject analysis set type	Full analysis
Subject analysis set description: The subjects with evaluable biomarkers at Day 1, subset of cells CD3- CD56+	
Subject analysis set title	Samples at day 21 / subset of cells CD3- CD56+
Subject analysis set type	Full analysis
Subject analysis set description: The subjects with evaluable biomarkers at Day 21, subset of cells CD3- CD56+	
Subject analysis set title	Samples at day 1 / subset of cells CD3- CD56+ bright CD16-
Subject analysis set type	Full analysis
Subject analysis set description: The subjects with evaluable biomarkers at Day 1, subset of cells CD3- CD56+ bright CD16-	
Subject analysis set title	Samples at day 21 / subset of cells CD3- CD56+ bright CD16-

Subject analysis set type	Full analysis

Subject analysis set description:

The subjects with evaluable biomarkers at Day 1, subset of cells CD3- CD56+ bright CD16-

Primary: CD3+ CD4+

End point title	CD3+ CD4+

End point description:

End point type	Primary

End point timeframe:

Day 1 and day 21 of cycle 1.

End point values	Samples with cell counts at day 1	Samples with cell counts at day 21		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	62	54		
Units: Counts in 10^9/L				
arithmetic mean (standard deviation)	0.43 (± 0.334)	0.59 (± 0.395)		

Statistical analyses

Statistical analysis title	Change from Day 1 to Day 21
Comparison groups	Samples with cell counts at day 1 v Samples with cell counts at day 21
Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.0007 [2]
Method	t-test, 2-sided

Notes:

[1] - 2-sided paired t-test at a significance level of 5% for the available samples with evaluable cell counts on day 1 and day 21. Subjects in the analysis for the paired t-test: 47

[2] - P-value to be compared to alpha-level 0.0083 (adjusted to multiplicity with respect to the Holm procedure).

Primary: CD3+ CD8+

End point title	CD3+ CD8+

End point description:

End point type	Primary

End point timeframe:

Day 1 and 21 of cycle1.

End point values	Samples with cell counts at day 1	Samples with cell counts at day 21		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	62	54		
Units: Counts in 10^9/L				
arithmetic mean (standard deviation)	0.4 (± 0.65)	0.32 (± 0.41)		

Statistical analyses

Statistical analysis title	Change from Day 1 to Day 21.
Comparison groups	Samples with cell counts at day 1 v Samples with cell counts at day 21
Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.1665 [4]
Method	t-test, 2-sided

Notes:

[3] - 2-sided paired t-test at a significance level of 5% for the available samples with evaluable cell counts on day 1 and day 21. Subjects in the analysis for the paired t-test: 47

[4] - P-value to be compared to alpha-level 0.05 (adjusted to multiplicity with respect to the Holm procedure).

Primary: CD3- CD56+

End point title	CD3- CD56+

End point description:

End point type	Primary

End point timeframe:

Day 1 and day 21 of cycle 1.

End point values	Samples with cell counts at day 1	Samples with cell counts at day 21		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	62	54		
Units: Counts 10^9/L				
arithmetic mean (standard deviation)	0.15 (± 0.132)	0.44 (± 0.385)		

Statistical analyses

Statistical analysis title	Change from Day 1 to day 21
Comparison groups	Samples with cell counts at day 21 v Samples with cell counts at day 1

Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	< 0.0001 [6]
Method	t-test, 2-sided

Notes:

[5] - 2-sided paired t-test at a significance level of 5% for the available samples with evaluable cell counts on day 1 and day 21. Subjects in the analysis for the paired t-test: 47

[6] - P-value to be compared to alpha-level 0.0071 (adjusted to multiplicity with respect to the Holm procedure).

Primary: Cd3zeta

End point title	Cd3zeta

End point description:

End point type	Primary

End point timeframe:

Day 1 and day 21 of cycle 1.

End point values	Samples at day 1 / subset of cells CD3+ CD4+	Samples at day 21 / subset of cells CD3+ CD4+	Samples at day 1 / subset of cells CD3+ CD8+	Samples at day 21 / subset of cells CD3+ CD8+
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	62	62	62	62
Units: Median fluorescence intensity				
arithmetic mean (standard deviation)	1119.42 (± 666.581)	1053.74 (± 425.445)	1224.52 (± 514.294)	1265.4 (± 540.521)

End point values	Samples at day 1 / subset of cells CD3- CD56+ dim CD16+	Samples at day 21 / subset of cells CD3- CD56+ dim CD16+		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	62	62		
Units: Median fluorescence intensity				
arithmetic mean (standard deviation)	2113.34 (± 963.493)	2129.1 (± 995.253)		

Statistical analyses

Statistical analysis title	Test of the day effect across all subsets.
Comparison groups	Samples at day 1 / subset of cells CD3+ CD4+ v Samples at day 21 / subset of cells CD3+ CD4+ v Samples at day 1 / subset of cells CD3+ CD8+ v Samples at day 21 / subset of cells CD3+ CD8+ v Samples at day 1 / subset of cells CD3- CD56+ dim CD16+ v Samples at day 21 / subset of cells CD3- CD56+ dim CD16+

Number of subjects included in analysis	372
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.1236 [8]
Method	Mixed models analysis

Notes:

[7] - Mixed models analysis of variance (ANOVA) for longitudinal data on the differences between day 1 and day 21 values. The models included Phenotype as fixed effect
and Patient as random effect. The overall day effect across all subsets was assessed by performing the test
of fixed effects on the phenotype. Number of subjects with evaluable biomarkers for the day 1 and day 21 in this analysis: 55

[8] - P-value to be compared to alpha-level 0.025 (adjusted to multiplicity with respect to the Holm procedure).

Primary: CD25+

End point title	CD25+

End point description:

End point type	Primary

End point timeframe:

Day 1 and day 21 of cycle 1.

End point values	Samples at day 1 / subset of cells CD3+ CD4+	Samples at day 21 / subset of cells CD3+ CD4+	Samples at day 1 / subset of cells CD3+ CD8+	Samples at day 21 / subset of cells CD3+ CD8+
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	62	62	62	62
Units: Percent				
arithmetic mean (standard deviation)	7.93 (± 7.009)	26.7 (± 13.846)	5.99 (± 9.626)	5.94 (± 7.432)

End point values	Samples at day 1 / subset of cells CD3- CD56+	Samples at day 21 / subset of cells CD3- CD56+		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	58	61		
Units: Percent				
arithmetic mean (standard deviation)	2.33 (± 3.516)	0.74 (± 1.144)		

Statistical analyses

Statistical analysis title	Test of the day effect across all subsets.
Comparison groups	Samples at day 21 / subset of cells CD3+ CD4+ v Samples at day 1 / subset of cells CD3+ CD8+ v Samples at day 1 / subset of cells CD3+ CD4+ v Samples at day 21 / subset of cells CD3+ CD8+ v Samples at day 1 / subset of cells CD3- CD56+

	v Samples at day 21 / subset of cells CD3- CD56+
Number of subjects included in analysis	367
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	< 0.0001 [10]
Method	Mixed models analysis

Notes:

[9] - Mixed models analysis of variance (ANOVA) for longitudinal data on the differences between day 1 and day 21 values. The models included Phenotype as fixed effect
and Patient as random effect. The overall day effect across all subsets was assessed by performing the test
of fixed effects on the phenotype. Number of subjects with evaluable biomarkers for the day 1 and day 21 in this analysis: 55

[10] - P-value to be compared to alpha-level 0.0056 (adjusted to multiplicity with respect to the Holm procedure).

Primary: CD69+

End point title	CD69+

End point description:

End point type	Primary

End point timeframe:

Day 1 and day 21 of cycle 1.

End point values	Samples at day 1 / subset of cells CD3+ CD4+	Samples at day 21 / subset of cells CD3+ CD4+	Samples at day 1 / subset of cells CD3+ CD8+	Samples at day 21 / subset of cells CD3+ CD8+
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	62	62	62	62
Units: Percent				
arithmetic mean (standard deviation)	14.22 (± 11.962)	13.12 (± 12.1)	21.41 (± 17.481)	18.61 (± 13.925)

End point values	Samples at day 1 / subset of cells CD3- CD56+	Samples at day 21 / subset of cells CD3- CD56+		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	62	62		
Units: Percent				
arithmetic mean (standard deviation)	18.3 (± 11.277)	13.73 (± 9.448)		

Statistical analyses

Statistical analysis title	Test of the day effect across all subsets.
Comparison groups	Samples at day 1 / subset of cells CD3+ CD4+ v Samples at day 21 / subset of cells CD3+ CD4+ v Samples at day 1 /

	subset of cells CD3+ CD8+ v Samples at day 21 / subset of cells CD3+ CD8+ v Samples at day 1 / subset of cells CD3- CD56+ v Samples at day 21 / subset of cells CD3- CD56+
Number of subjects included in analysis	372
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	= 0.0057 [12]
Method	Mixed models analysis

Notes:

[11] - Mixed models analysis of variance (ANOVA) for longitudinal data on the differences between Day 1
and Day 21 values. The models included Phenotype as fixed effect
and Patient as random effect. The overall Day effect across all subsets was assessed by performing the test
of fixed effects on the phenotype. Number of subjects with evaluable biomarkers for the day 1 and day 21 in this analysis: 55

[12] - P-value to be compared to alpha-level 0.0125 (adjusted to multiplicity with respect to the Holm procedure).

Primary: IFN-gamma+

End point title	IFN-gamma+

End point description:

End point type	Primary

End point timeframe:

Day 1 and day 21 of cycle 1.

End point values	Samples at day 1 / subset of cells CD3+ CD4+	Samples at day 21 / subset of cells CD3+ CD4+	Samples at day 1 / subset of cells CD3+ CD8+	Samples at day 21 / subset of cells CD3+ CD8+
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	58	62	58	62
Units: Percent				
arithmetic mean (standard deviation)	21.28 (± 15.725)	18.82 (± 16.401)	58.17 (± 24.432)	59.97 (± 20.454)

End point values	Samples at day 1 / subset of cells CD3- CD56+	Samples at day 21 / subset of cells CD3- CD56+		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	58	62		
Units: Percent				
arithmetic mean (standard deviation)	47.75 (± 21.738)	50.87 (± 18.241)		

Statistical analyses

Statistical analysis title	Test of the day effect across all subsets.
Comparison groups	Samples at day 21 / subset of cells CD3+ CD4+ v Samples at day 1 / subset of cells CD3+ CD8+ v Samples at day 21 / subset of cells CD3+ CD8+ v Samples at day 1 / subset of cells CD3- CD56+ v Samples at day 1 / subset of cells CD3+ CD4+ v Samples at day 21 / subset of cells CD3- CD56+
Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	other[13]
P-value	= 0.0007 [14]
Method	Mixed models analysis

Notes:

[13] - Mixed models analysis of variance (ANOVA) for longitudinal data on the differences between Day 1
and Day 21 values. The models included Phenotype as fixed effect
and Patient as random effect. The overall Day effect across all subsets was assessed by performing the test
of fixed effects on the phenotype. Number of subjects with evaluable biomarkers for the day 1 and day 21 in this analysis: 55

[14] - P-value to be compared to alpha-level 0.01 (adjusted to multiplicity with respect to the Holm procedure).

Primary: NKp46

End point title	NKp46

End point description:

End point type	Primary

End point timeframe:

Day 1 and day 21 of cycle 1.

End point values	Samples at day 1 / subset of cells CD3- CD56+ dim CD16+	Samples at day 21 / subset of cells CD3- CD56+ dim CD16+	Samples at day 1 / subset of cells CD3- CD56+ bright CD16-	Samples at day 21 / subset of cells CD3- CD56+ bright CD16-
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	62	62	62	62
Units: Median fluorescence intensity				
arithmetic mean (standard deviation)	707.55 (± 443.458)	1081.76 (± 579.131)	955.59 (± 697.57)	985.45 (± 698.282)

Statistical analyses

Statistical analysis title	Test of the day effect across all subsets.
Comparison groups	Samples at day 1 / subset of cells CD3- CD56+ dim CD16+ v Samples at day 21 / subset of cells CD3- CD56+ dim CD16+ v Samples at day 1 / subset of cells CD3- CD56+ bright CD16- v Samples at day 21 / subset of cells CD3- CD56+ bright CD16-

Number of subjects included in analysis	248
Analysis specification	Pre-specified
Analysis type	other[15]
P-value	< 0.0001 [16]
Method	Mixed models analysis

Notes:

[15] - Mixed models analysis of variance (ANOVA) for longitudinal data on the differences between Day 1
and Day 21 values. The models included Phenotype as fixed effect
and Patient as random effect. The overall Day effect across all subsets was assessed by performing the test
of fixed effects on the phenotype. Number of subjects with evaluable biomarkers for the day 1 and day 21 in this analysis: 55

[16] - P-value to be compared to alpha-level 0.0063 (adjusted to multiplicity with respect to the Holm procedure).

Primary: NKp30

End point title	NKp30

End point description:

End point type	Primary

End point timeframe:

Day 1 and day 21 of cycle 1.

End point values	Samples at day 1 / subset of cells CD3- CD56+ dim CD16+	Samples at day 21 / subset of cells CD3- CD56+ dim CD16+	Samples at day 1 / subset of cells CD3- CD56+ bright CD16-	Samples at day 21 / subset of cells CD3- CD56+ bright CD16-
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	62	62	62	62
Units: Median fluorescence intensity				
arithmetic mean (standard deviation)	391.38 (± 201.465)	493.21 (± 198.144)	418.69 (± 156.635)	580.34 (± 205.83)

Statistical analyses

Statistical analysis title	Test of the day effect across all subsets.
Comparison groups	Samples at day 1 / subset of cells CD3- CD56+ dim CD16+ v Samples at day 21 / subset of cells CD3- CD56+ dim CD16+ v Samples at day 1 / subset of cells CD3- CD56+ bright CD16- v Samples at day 21 / subset of cells CD3- CD56+ bright CD16-
Number of subjects included in analysis	248
Analysis specification	Pre-specified
Analysis type	other[17]
P-value	< 0.0001 [18]
Method	Mixed models analysis

Notes:

[17] - Mixed models analysis of variance (ANOVA) for longitudinal data on the differences between Day 1
and Day 21 values. The models included Phenotype as fixed effect
and Patient as random effect. The overall Day effect across all subsets was assessed by performing the

test
of fixed effects on the phenotype. Number of subjects with evaluable biomarkers for the day 1 and day 21 in this analysis: 55
[18] - P-value to be compared to alpha-level 0.005 (adjusted to multiplicity with respect to the Holm procedure).

Primary: NKG2D

End point title	NKG2D
End point description:	
End point type	Primary
End point timeframe:	
Day 1 and day 21 of cycle 1.	

End point values	Samples at day 1 / subset of cells CD3- CD56+ dim CD16+	Samples at day 21 / subset of cells CD3- CD56+ dim CD16+	Samples at day 1 / subset of cells CD3- CD56+ bright CD16-	Samples at day 21 / subset of cells CD3- CD56+ bright CD16-
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	60	61	60	61
Units: Median fluorescence intensity				
arithmetic mean (standard deviation)	1700.6 (± 920.939)	1868.02 (± 1027.784)	2504.17 (± 1228.668)	2513.34 (± 1284.663)

Statistical analyses

Statistical analysis title	Test of the day effect across all subsets.
Comparison groups	Samples at day 21 / subset of cells CD3- CD56+ dim CD16+ v Samples at day 1 / subset of cells CD3- CD56+ bright CD16- v Samples at day 1 / subset of cells CD3- CD56+ dim CD16+ v Samples at day 21 / subset of cells CD3- CD56+ bright CD16-
Number of subjects included in analysis	242
Analysis specification	Pre-specified
Analysis type	other[19]
P-value	= 0.10013 [20]
Method	Mixed models analysis

Notes:
[19] - Mixed models analysis of variance (ANOVA) for longitudinal data on the differences between Day 1
and Day 21 values. The models included Phenotype as fixed effect
and Patient as random effect. The overall Day effect across all subsets was assessed by performing the test
of fixed effects on the phenotype. Number of subjects with evaluable biomarkers for the day 1 and day 21 in this analysis: 54
[20] - P-value to be compared to alpha-level 0.0167 (adjusted to multiplicity with respect to the Holm procedure).

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The duration of the treatment phase per patient was approximately 18 months. Patients were followed for relapse for up to 2 years (after enrollment) or until death, whichever came first.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14

Reporting groups

Reporting group title	Safety population

Reporting group description: -

Serious adverse events	Safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 84 (16.67%)		
number of deaths (all causes)	29		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Quadriparesis			
subjects affected / exposed	1 / 84 (1.19%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	6 / 84 (7.14%)		
occurrences causally related to treatment / all	4 / 8		
deaths causally related to treatment / all	0 / 0		
Chills			
subjects affected / exposed	1 / 84 (1.19%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	1 / 84 (1.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	1 / 84 (1.19%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Enteritis			
subjects affected / exposed	1 / 84 (1.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastritis			
subjects affected / exposed	1 / 84 (1.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 84 (1.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	1 / 84 (1.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pharyngitis			
subjects affected / exposed	1 / 84 (1.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumococcal sepsis			
subjects affected / exposed	1 / 84 (1.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 84 (1.19%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	3 / 84 (3.57%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	2 / 84 (2.38%)		
occurrences causally related to treatment / all	0 / 2		
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	82 / 84 (97.62%)		
Vascular disorders			
Flushing			
subjects affected / exposed	42 / 84 (50.00%)		
occurrences (all)	55		
Hypotension			
subjects affected / exposed	9 / 84 (10.71%)		
occurrences (all)	15		
Cardiac disorders			
Palpitations			
subjects affected / exposed	6 / 84 (7.14%)		
occurrences (all)	8		
Nervous system disorders			
Headache			
subjects affected / exposed	30 / 84 (35.71%)		
occurrences (all)	54		
Dizziness			
subjects affected / exposed	8 / 84 (9.52%)		
occurrences (all)	11		

General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	26 / 84 (30.95%)		
occurrences (all)	28		
Injection site reaction			
subjects affected / exposed	25 / 84 (29.76%)		
occurrences (all)	46		
Injection site nodule			
subjects affected / exposed	18 / 84 (21.43%)		
occurrences (all)	28		
Injection site erythema			
subjects affected / exposed	15 / 84 (17.86%)		
occurrences (all)	18		
Injection site pain			
subjects affected / exposed	8 / 84 (9.52%)		
occurrences (all)	8		
Granuloma			
subjects affected / exposed	8 / 84 (9.52%)		
occurrences (all)	8		
Pyrexia			
subjects affected / exposed	39 / 84 (46.43%)		
occurrences (all)	57		
Asthenia			
subjects affected / exposed	5 / 84 (5.95%)		
occurrences (all)	6		
Chest discomfort			
subjects affected / exposed	5 / 84 (5.95%)		
occurrences (all)	5		
Chills			
subjects affected / exposed	9 / 84 (10.71%)		
occurrences (all)	15		
Blood and lymphatic system disorders			
Eosinophilia			
subjects affected / exposed	28 / 84 (33.33%)		
occurrences (all)	30		
Gastrointestinal disorders			

Nausea subjects affected / exposed occurrences (all)	17 / 84 (20.24%) 25		
Diarrhoea subjects affected / exposed occurrences (all)	8 / 84 (9.52%) 12		
Abdominal pain upper subjects affected / exposed occurrences (all)	6 / 84 (7.14%) 9		
Vomiting subjects affected / exposed occurrences (all)	5 / 84 (5.95%) 6		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	13 / 84 (15.48%) 20		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	12 / 84 (14.29%) 13		
Night sweats subjects affected / exposed occurrences (all)	5 / 84 (5.95%) 6		
Pruritus subjects affected / exposed occurrences (all)	6 / 84 (7.14%) 7		
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	5 / 84 (5.95%) 5		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	10 / 84 (11.90%) 10		
Myalgia			

subjects affected / exposed	8 / 84 (9.52%)		
occurrences (all)	8		
Back pain			
subjects affected / exposed	7 / 84 (8.33%)		
occurrences (all)	8		
Muscle spasms			
subjects affected / exposed	5 / 84 (5.95%)		
occurrences (all)	5		
Musculoskeletal pain			
subjects affected / exposed	6 / 84 (7.14%)		
occurrences (all)	6		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	25 / 84 (29.76%)		
occurrences (all)	48		
Bronchitis			
subjects affected / exposed	5 / 84 (5.95%)		
occurrences (all)	5		
Upper respiratory tract infection			
subjects affected / exposed	7 / 84 (8.33%)		
occurrences (all)	9		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 December 2009	Amendment to Study Protocol (Version 2.0) 1) To allow for quantitative measure-ments of genetic markers of AML using molecular techniques for assessment of minimal residual disease (MRD) 2) To allow for patients enrollment with-out consolidation therapy
01 August 2011	Amendment to Study Protocol (Version 3.0) 1) Expand the allowable window of time between the end of consolidation therapy to enrollment from 8 to 12 weeks. 2) Define "evaluable patient" for the vari-ous study endpoints 3) Clarify timing aspects regarding the planned interim analysis. 4) Eliminate the inclusion criterion for partial thromboplastin time (PTT) within normal limits. 5) Drop the requirement to determine per-formance status by criteria other than Karnofsky score

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
20 August 2012	organisational reasons after transfer of sponsorship: halt of recruitment, patients already included continued according to protocol	-

Notes:

Limitations and caveats

None reported