

**Clinical trial results:****Open-label, Multicenter Phase I/II Study: Salvage Therapy of Progressive and Relapsed Aggressive Non-Hodgkin-Lymphoma by Combination of Lenalidomide (Revlimid®) with Rituximab, Dexamethason, High-dose ARA-C and Cisplatinum****Summary**

EudraCT number	2009-010824-25
Trial protocol	DE
Global end of trial date	08 April 2015

Results information

Result version number	v1 (current)
This version publication date	15 December 2022
First version publication date	15 December 2022

Trial information**Trial identification**

Sponsor protocol code	34 DSHNHL 2008-R6
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02983097
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GMIHO Gesellschaft für Medizinische Innovation – Hämatologie und Onkologie mbH
Sponsor organisation address	Almstadtstraße 7, Berlin, Germany, 10119
Public contact	Medical Consulting, GMIHO Gesellschaft für Medizinische Innovation – Hämatologie und Onkologie mbH, 0049 35125933100, info@gmiho.de
Scientific contact	Medical Consulting, GMIHO Gesellschaft für Medizinische Innovation – Hämatologie und Onkologie mbH, 0049 35125933100, info@gmiho.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	31 December 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 December 2013
Global end of trial reached?	Yes
Global end of trial date	08 April 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To provide efficient remission induction in second line treatment of aggressive NHL giving a higher fraction of patients the chance to achieve remission and subsequently to receive salvage therapy (autologous or allogeneic SCT)

Protection of trial subjects:

The conduct of this study was in compliance with the Good Clinical Practice Guidelines and under the guiding principles detailed in the Declaration of Helsinki. The study was also carried out in keeping with applicable local law(s) and regulation(s).

Patients were closely evaluated for toxicity.

In patients with significant neurotoxicity from first line treatment or other neurologic impairment, vincristine should be omitted and may be replaced by a single dose cyclophosphamide 100 mg/m². The purpose of the prephase treatment was to prevent tumour lysis syndrome in patients with extensive tumors, to improve the performance status of the patient and to reduce the toxicity of the first chemotherapy cycle.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 November 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 35
Worldwide total number of subjects	35
EEA total number of subjects	35

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)	29
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

From 11th November 2010 through 30th October 2013 a total of 35 patients were enrolled in phase I of the study at 6 of 13 participating centers in Germany. Thereof, 34 patients were dosed in 5 cohorts.

Pre-assignment

Screening details:

Six cohorts of minimum 6 patients each to be treated at maximal 5 dose levels (0-4) were planned. In cohorts 3 to 6, additional patients were to be recruited to ensure at least 18 eligible therapy cycles.

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	Treatment period
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	
Other name	Revlimid®
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

At dose level 0 three cycles of R2-DHAP were to be given, the first cycle was R- DHAP alone followed by cycle 2 and 3 supplemented with lenalidomide 5 mg/d at days 1 to 7. Mobilization of stem cells was done after cycle one or two of R²-DHAP. Therapy was repeated every 21 days.

At dose levels 1 to 2 lenalidomide was given at days 1 to 7 at a dose of 5 mg/d or 15 mg/d, respectively. At dose level 4, 15 mg of lenalidomide was to be given from day -6 to day 7. At dose level 5 20 mg of lenalidomide was to be given from day -6 to day 7.

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

Dosage and administration details:

Rituximab plus DHAP was given as usual: Rituximab 375 mg/m² on day 1. Therapy was repeated every 21 days.

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

Dosage and administration details:

Cisplatinum 100 mg/m² on day 2. Therapy was repeated every 21 days.

Investigational medicinal product name	Cytarabine
Investigational medicinal product code	
Other name	ARA-C

Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details:	
ARA-C 2 x 2000 mg/m ² on day 3. Therapy was repeated every 21 days.	
Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	Cytarabine
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Dexamethasone 40 mg on days 2 to 5. Therapy was repeated every 21 days.

Number of subjects in period 1	Treatment period
Started	35
Completed	34
Not completed	1
Protocol deviation	1

Baseline characteristics

Reporting groups

Reporting group title	overall trial
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Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	35	35	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	29	29	
From 65-84 years	6	6	
85 years and over	0	0	
Gender categorical			
Units: Subjects			
Female	13	13	
Male	22	22	

End points

End points reporting groups

Reporting group title	Treatment period
Reporting group description: -	

Primary: Maximal tolerable dose

End point title	Maximal tolerable dose ^[1]
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End point description:

The following algorithm was used to establish the MTD: At least six patients were planned to be treated in each of 6 cohorts.

- If no serious toxicity (see below) occurred, the next cohort was treated at the next higher dose level.
- If one case of serious toxicity occurred, the next cohort of patients was treated at the same dose level.
- If two or more cases of serious toxicity occurred, the next cohort was treated at the next lower dose level; if this would have occurred at dose level 0, the study was to be terminated.

End point type	Primary
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End point timeframe:

18 cycles at every dose level

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: The phase I part of the study was conducted to determine the dose of lenalidomide given together with R-DHAP. Data from dose escalation of the study showed evidence for the feasibility and safety of adding lenalidomide to a combination of standard R-DHAP. Dose level 2 (15 mg lenalidomide on days 1 to 7) was assessed as the maximum tolerable dose of lenalidomide given in combination with standard R-DHAP.

End point values	Treatment period			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: Number of patients				
Cohort 1	6			
Cohort 2	6			
Cohort 3	7			
Cohort 4	8			
Cohort 5	7			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

from day 1 to day 85

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	13.1
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Frequency threshold for reporting non-serious adverse events: 0 %

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: In total, 51 AEs were documented for 22 out of 34 patients included in the safety analysis set (64.7%). Most frequently reported AEs were hypokalemia (5 events), leukopenia (3 events), thrombocytopenia (3 events). Among the AEs, 14 were serious (SAEs) and occurred in 10 patients. For 3 of them a relationship to treatment with lenalidomide was assessed as at least possible and unexpected (SUSAR) including the dose-limiting toxicity of one patient.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 May 2012	Version 9.0 dated 23 Jul 2012 (Amendment 1) Changes: - Revise of exclusion criteria bone marrow involvement > 25%. CNS involvement has become exclusion criteria instead. - Disruption of treatment due to lymphoma progress was excluded as a toxicity event - With regards to published data of other trials biometry of the trial has been revised in due consideration of interpretability. The mode of analysis has been changed. Analysis will be performed on a per-therapy-cycle instead of a per-patient basis. At least 18 evaluable cycles have to be available for analysis to complete a patient cohort; therefore at least 6 patients have to be recruited in each cohort. If patients drop out of the study prematurely, or if any therapy cycle is deemed not evaluable, additional patients will be recruited as to fulfill the criterion of having a minimum of 18 evaluable therapy cycles.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was terminated by 8 April 2015 after successfully completing and analyzing part I of the study due to emerging, more promising treatment options apart from R-DHAP.

Notes: