Clinical trial results:
Cardiotoxicity with rituximab, cyclophosphamide, non-pegylated liposomal doxorubicin, vincristine and prednisolone compared to rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone in frontline treatment of patients with diffuse large B-cell lymphoma. (NHL-14)

Summary

EudraCT number	2007-004970-24
Trial protocol	AT
Global end of trial date	13 January 2012

Results information

Result version number	v1 (current)
This version publication date	29 July 2016
First version publication date	29 July 2016

Trial information

Trial identification

Sponsor protocol code	NHL-14

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00575406
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AGMT
Sponsor organisation address	Gentzgasse 60/20, Vienna, Austria, 1180
Public contact	Daniela Wolkersdorfer, AGMT, 0043 6626404411, d.wolkersdorfer@agmt.at
Scientific contact	Richard Greil, AGMT, 0043 5725525801, r.greil@salk.at

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	13 January 2012
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 January 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to compare the R-CHOP regimen with the R-COMP regimen, where doxorubicin was substituted by non-pegylated liposomal doxorubicin, in order to determine cardiotoxicty.
Cardiotoxicity was measured by LVEF according to a modified version of Simpson’s method (ultrasound).

Protection of trial subjects:

Safety was monitored by reporting of clinical adverse events.

Background therapy:

Rituximab, Cyclophosphamide, Vincristine, Prednisolone

Evidence for comparator:

Chemoimmunotherapy containing rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) is the standard treatment for diffuse large B-cell lymphoma (DLBCL). Doxorubicin may induce early and late cardiotoxicity. Non-pegylated liposomal doxorubicin may reduce this.

Actual start date of recruitment	21 December 2007
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	Austria: 94
Worldwide total number of subjects	94
EEA total number of subjects	94

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)	45

From 65 to 84 years	49
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between December 2007 and July 2010 94 patients were enrolled at 10 sites in Austria.

Pre-assignment

Screening details:

Patients older than 18 years, with histologically confirmed and untreated CD20-positive DLBCL in any stage of the disease were eligible.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	R-COMP

Arm description:

Standard R-CHOP regimen with NPL-doxorubicin replacing doxorubicin, 6 cycles in 3 weekly intervals.

Arm type	Experimental
Investigational medicinal product name	NPL-doxorubicin
Investigational medicinal product code	
Other name	Myocet(R)
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

50 mg/m² NPL-doxorubicin
Rituximab, cyclophosphamide, vincristine, prednisolon in standard dosage

Arm title	R-CHOP

Arm description:

R-CHOP with conventional doxorubicin, 6 cycles in 3 weekly intervals.

Arm type	Active comparator
Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

50 mg/m² Doxorubicin
Rituximab, cyclophosphamide, vincristine, prednisolon in standard dosage

Arm title	R-COMP non-randomized

Arm description:

Standard R-CHOP regimen with NPL-doxorubicin replacing doxorubicin, 6 cycles in 3 weekly intervals.

Arm type	Experimental
Investigational medicinal product name	NPL-doxorubicin
Investigational medicinal product code	
Other name	Myocet(R)
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

50 mg/m² NPL-doxorubicin
Rituximab, cyclophosphamide, vincristine, prednisolon in standard dosage

Number of subjects in period 1[1]	R-COMP	R-CHOP	R-COMP non-randomized
Started	40	39	6
Completed	34	29	3
Not completed	6	10	3
Consent withdrawn by subject	2	-	-
Physician decision	3	1	-
Adverse event, non-fatal	1	7	-
Death	-	-	2
Lack of efficacy	-	2	-
Protocol deviation	-	-	1

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: Following patients were excluded from ITT analyses:
R-COMP arm: 3 patients (1 ineligible after central histologic review; 1 CNS involvement; 1 HIV positivity)
R-CHOP arm: 6 patients (6 ineligible after central histologic review)
R-COMP non-randomized arm: Subjects with myocardial infarction 6 month before study entry or heart insufficiency (NYHA 3 or 4) were not randomized but enrolled directly to this arm. These patients were not part of ITT.

Baseline characteristics

Reporting groups	
Reporting group title	R-COMP
Reporting group description:	
Standard R-CHOP regimen with NPL-doxorubicin replacing doxorubicin, 6 cycles in 3 weekly intervals.	
Reporting group title	R-CHOP
Reporting group description:	
R-CHOP with conventional doxorubicin, 6 cycles in 3 weekly intervals.	
Reporting group title	R-COMP non-randomized
Reporting group description:	
Standard R-CHOP regimen with NPL-doxorubicin replacing doxorubicin, 6 cycles in 3 weekly intervals.	

Reporting group values	R-COMP	R-CHOP	R-COMP non-randomized
Number of subjects	40	39	6
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	65	65	70.5
full range (min-max)	18 to 81	22 to 84	65 to 83
Gender categorical Units: Subjects			
Female	17	17	3
Male	23	22	3

Reporting group values	Total		
Number of subjects	85		
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 full range (min-max)	- 		
Gender categorical Units: Subjects			
Female	37		
Male	48		

End points

End points reporting groups

Reporting group title	R-COMP
Reporting group description:	
Standard R-CHOP regimen with NPL-doxorubicin replacing doxorubicin, 6 cycles in 3 weekly intervals.	
Reporting group title	R-CHOP
Reporting group description:	
R-CHOP with conventional doxorubicin, 6 cycles in 3 weekly intervals.	
Reporting group title	R-COMP non-randomized
Reporting group description:	
Standard R-CHOP regimen with NPL-doxorubicin replacing doxorubicin, 6 cycles in 3 weekly intervals.	

Primary: LVEF over all treatment cycles

End point title	LVEF over all treatment cycles[1][2]
End point description:	
End point type	Primary
End point timeframe:	
Pre-treatment to 4-8 weeks after last cycle	

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 randomised controlled trial revealed no significant difference in the primary end-point, defined as mean LVEF over all treatment cycles by substituting doxorubicin in the R-CHOP regimen with a comparable dose of NPL-doxorubicin. (P-value 0.167)

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Arm 3 (R-COMP non-randomized) was not designed for primary endpoint analyses.

End point values	R-COMP	R-CHOP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40[3]	39[4]		
Units: % LVEF				
arithmetic mean (standard deviation)	63.3 (± 6.3)	62.2 (± 7.8)		

Notes:

[3] - 178 measurements

[4] - 158 measurements

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs were recorded by the investigator from the time the subject signs informed consent to final examination.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	All enrolled patients

Reporting group description:

Serious adverse events are reported from all enrolled patients (including non-randomised patients receiving R-COMP)

Serious adverse events	All enrolled patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	51 / 94 (54.26%)		
number of deaths (all causes)	4		
number of deaths resulting from adverse events	2		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertensive crisis			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombosis			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Chest pain			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Death			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
General physical health deterioration			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Influenza like illness			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oedema			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	9 / 94 (9.57%)		
occurrences causally related to treatment / all	5 / 10		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Cough			

subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
C-reactive protein increased			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Angina unstable			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac arrest			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Cardiac failure			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Right ventricular failure			

subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			
Central nervous system lesion			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dizziness			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Migraine			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	5 / 94 (5.32%)		
occurrences causally related to treatment / all	2 / 6		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	10 / 94 (10.64%)		
occurrences causally related to treatment / all	12 / 13		
deaths causally related to treatment / all	0 / 1		
Leukopenia			

subjects affected / exposed	2 / 94 (2.13%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	3 / 94 (3.19%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				
subjects affected / exposed	1 / 94 (1.06%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Ear and labyrinth disorders				
Vertigo				
subjects affected / exposed	1 / 94 (1.06%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Colitis				
subjects affected / exposed	2 / 94 (2.13%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	2 / 94 (2.13%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	4 / 94 (4.26%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Diarrhoea haemorrhagic				
subjects affected / exposed	1 / 94 (1.06%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Ileus				

subjects affected / exposed	2 / 94 (2.13%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	1 / 1			
Nausea				
subjects affected / exposed	1 / 94 (1.06%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rectal haemorrhage				
subjects affected / exposed	1 / 94 (1.06%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ulcus ventriculi				
subjects affected / exposed	1 / 94 (1.06%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	1 / 94 (1.06%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Micturition disorder				
subjects affected / exposed	1 / 94 (1.06%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary incontinence				
subjects affected / exposed	1 / 94 (1.06%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Arthralgia				
subjects affected / exposed	1 / 94 (1.06%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Bone pain				
subjects affected / exposed	2 / 94 (2.13%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pathological fracture				
subjects affected / exposed	1 / 94 (1.06%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal pain				
subjects affected / exposed	1 / 94 (1.06%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Bronchitis				
subjects affected / exposed	1 / 94 (1.06%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Catheter site infection				
subjects affected / exposed	1 / 94 (1.06%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Erysipelas				
subjects affected / exposed	2 / 94 (2.13%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Febrile infection				
subjects affected / exposed	2 / 94 (2.13%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis norovirus				
subjects affected / exposed	1 / 94 (1.06%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infection				

subjects affected / exposed	2 / 94 (2.13%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Oral herpes				
subjects affected / exposed	1 / 94 (1.06%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pharyngitis				
subjects affected / exposed	1 / 94 (1.06%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	4 / 94 (4.26%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 1			
Pseudomonal sepsis				
subjects affected / exposed	1 / 94 (1.06%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection fungal				
subjects affected / exposed	1 / 94 (1.06%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rhinitis				
subjects affected / exposed	1 / 94 (1.06%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	1 / 94 (1.06%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Sinusitis				

subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	All enrolled patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	94 / 94 (100.00%)		
Blood and lymphatic system disorders			
NA	Additional description: Data is summarized in publication		
subjects affected / exposed	94 / 94 (100.00%)		
occurrences (all)	94		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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/26990931