Clinical trial results:
A phase II multicenter open-label study of MabThera (Rituximab) addition to regularly prescribed chemotherapy in patients with untreated Mantle Cell Lymphoma

Summary

EudraCT number	2009-011433-27
Trial protocol	RO
Global end of trial date	19 August 2014

Results information

Result version number	v1 (current)
This version publication date	17 May 2017
First version publication date	17 May 2017

Trial information

Trial identification

Sponsor protocol code	ML22489

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01144403
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.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	19 August 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 August 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To determine Overall Response Rate (ORR) (expressed as complete response [CR] and partial response [PR]) in Mantle Cell Lymphoma (MCL) subjects treated with MabThera plus chemotherapy. The percentage of subjects who achieve CR/ unconfirmed complete (CRu) or PR while on rituximab induction therapy will be assessed.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 June 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	24 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Romania: 8
Worldwide total number of subjects	8
EEA total number of subjects	8

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)	7
From 65 to 84 years	1

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total 8 subjects were enrolled from Romania.

Period 1

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

Arms

Arm title	Rituximab

Arm description:

Rituximab, 375 milligram per metre square (mg/m^2) was given intravenously on Day 1 and then every 28 days (+/7 days) for 6 cycles, followed by 2 consolidated infusions in responders as rituximab induction therapy. Rituximab infusions were administered concomitantly with prescribed chemotherapy i.e., fludarabine, cyclophosphamide and mitoxantrone (maximum 6 cycles). Cyclophosphamide: as prescribed, 6 cycles Fludarabine: as prescribed, 6 cycles Mitoxantrone: as prescribed, 6 cycles Rituximab [Mabthera/Rituxan]: 375 mg/m^2 intravenously, Day 1 of each 28-day cycle, up to 8 cycles.

Arm type	Experimental
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	Mabthera, Rituxan
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Rituximab 375 mg/m^2 was administered intravenously, Day 1 of each 28-day cycle, up to 8 cycles.

Number of subjects in period 1	Rituximab
Started	8
Completed	3
Not completed	5
Adverse Event	1
Death	1
Lost to follow-up	3

Baseline characteristics

Reporting groups	
Reporting group title	Rituximab

Reporting group description:

Rituximab, 375 milligram per metre square (mg/m^2) was given intravenously on Day 1 and then every 28 days (+/7 days) for 6 cycles, followed by 2 consolidated infusions in responders as rituximab induction therapy. Rituximab infusions were administered concomitantly with prescribed chemotherapy i.e., fludarabine, cyclophosphamide and mitoxantrone (maximum 6 cycles). Cyclophosphamide: as prescribed, 6 cycles Fludarabine: as prescribed, 6 cycles Mitoxantrone: as prescribed, 6 cycles Rituximab [Mabthera/Rituxan]: 375 mg/m^2 intravenously, Day 1 of each 28-day cycle, up to 8 cycles.

Reporting group values	Rituximab	Total	
Number of subjects	8	8	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 60.5 ± 7.964	 -	
Gender categorical Units: Subjects			
Female	3	3	
Male	5	5	

End points

End points reporting groups

Reporting group title	Rituximab

Reporting group description:

Rituximab, 375 milligram per metre square (mg/m^2) was given intravenously on Day 1 and then every 28 days (+/7 days) for 6 cycles, followed by 2 consolidated infusions in responders as rituximab induction therapy. Rituximab infusions were administered concomitantly with prescribed chemotherapy i.e., fludarabine, cyclophosphamide and mitoxantrone (maximum 6 cycles). Cyclophosphamide: as prescribed, 6 cycles Fludarabine: as prescribed, 6 cycles Mitoxantrone: as prescribed, 6 cycles Rituximab [Mabthera/Rituxan]: 375 mg/m^2 intravenously, Day 1 of each 28-day cycle, up to 8 cycles.

Primary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)[1]

End point description:

Overall Response Rate (ORR) was determined by tumor response according to International Workshop Group to Standardize Response Criteria for mantle cell lymphoma (MCL) criteria from confirmed evaluations of both target, radiographically evaluated, and non-target lesions. A responder is defined as a subject experiencing either a complete (CR)/ unconfirmed complete (Cru), or partial response (PR) by these criteria. As per criteria; CR = disappearance of all evidence of disease; CRu = the sum of the product of the diameters (SPD) of multiple nodes decreased by at least 75%; PR = regression of measurable disease and no new sites. Efficacy population included all the subjects who had received at least one dose of study treatment.

End point type	Primary

End point timeframe:

Up to 50 months (approximately)

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: Only descriptive data was planned to be reported.

End point values	Rituximab			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: percentage of subjects				
number (not applicable)	87.5			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall survival is defined as time from date of enrollment to the date of death, regardless of the cause of death. Efficacy population included all the subjects who had received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

From the time of enrollment until death due to any cause (up to 50 months [approximately])

End point values	Rituximab			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: days				
median (confidence interval 95%)	927 (0 to 2204.066)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS)

End point title	Progression-free Survival (PFS)

End point description:

PFS is defined as the interval between the day of enrollment and the first documentation of progressive disease or death. Progression of disease is defined as at least a 20 percent (%) increase in the sum of longest diameter (LD) of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of 1 or more new lesions. Efficacy population included all the subjects who had received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

From the time of enrollment until death due to any cause (up to 50 months [approximately])

End point values	Rituximab			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: days				
median (confidence interval 95%)	653 (537.058 to 768.942)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subject With Adverse Event (AE)

End point title	Number of Subject With Adverse Event (AE)

End point description:

An AE was defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which did not necessarily have to have a causal relationship with study treatment. Safety population included all the subjects who had received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Up to 50 months (approximately)

End point values	Rituximab			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: subjects	8			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 50 months

Adverse event reporting additional description:

Safety population included all the subjects who had received at least one dose of study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups

Reporting group title	Rituximab

Reporting group description:

Rituximab, 375 milligram per metre square (mg/m^2) was given intravenously on Day 1 and then every 28 days (+/7 days) for 6 cycles, followed by 2 consolidated infusions in responders as rituximab induction therapy. Rituximab infusions were administered concomitantly with prescribed chemotherapy i.e., fludarabine, cyclophosphamide and mitoxantrone (maximum 6 cycles). Cyclophosphamide: as prescribed, 6 cycles Fludarabine: as prescribed, 6 cycles Mitoxantrone: as prescribed, 6 cycles Rituximab [Mabthera/Rituxan]: 375 mg/m^2 intravenously, Day 1 of each 28-day cycle, up to 8 cycles.

Serious adverse events	Rituximab		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 8 (37.50%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Toxicity			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Neutropenia			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 8 (12.50%)		
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	Rituximab		
Total subjects affected by non-serious adverse events subjects affected / exposed	8 / 8 (100.00%)		
Injury, poisoning and procedural complications Drug Eruption subjects affected / exposed occurrences (all)	2 / 8 (25.00%) 3		
Vascular disorders Ascending Aorta Dilatation subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Cardiac disorders Supraventricular arrhythmia subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Nervous system disorders Vertiginous syndrome subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Blood and lymphatic system disorders Anemia subjects affected / exposed occurrences (all)	3 / 8 (37.50%) 5		
Leucopenia subjects affected / exposed occurrences (all)	4 / 8 (50.00%) 7		
Neutropenia subjects affected / exposed occurrences (all)	2 / 8 (25.00%) 2		
ß2-microglobuline			

subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
C-reactive protein			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	2		
Thrombocytopenia			
subjects affected / exposed	5 / 8 (62.50%)		
occurrences (all)	6		
Gastrointestinal disorders			
Gastric Pain			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Tracheitis			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Respiratory Virosis			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Hepatobiliary disorders			
Hepatitis Ag HBS+			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Dermatitis Eczematous			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Infections and infestations			
Herpes			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Oral Candidiasis			

subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Metabolism and nutrition disorders Hyperglycemia subjects affected / exposed occurrences (all)	 1 / 8 (12.50%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 July 2010	Added 6 new sites and 6 new investigators to the study.
06 June 2011	Protocol version 2.0/14.09.2010

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.

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.
The study was prematurely terminated with 8 subjects enrolled, all of them were included into the statistical analyses.

Notes: