Clinical trial results:
A multicenter, phase III, open-label study evaluating the benefit of a long-term MabThera® (rituximab) maintenance therapy in patients with advanced follicular lymphoma after induction of response (CR(u) or PR) with MabThera® (rituximab) containing first-line regimen

Summary

EudraCT number	2005-000359-13
Trial protocol	HU
Global end of trial date	12 August 2013

Results information

Result version number	v1 (current)
This version publication date	18 March 2016
First version publication date	18 March 2016

Trial information

Trial identification

Sponsor protocol code	ML18167

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
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	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, 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	12 August 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 August 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluation of the efficacy and safety of a long-term MabThera® (rituximab) maintenance therapy in patients with advanced follicular lymphoma after induction of response (CR(u) or PR) with a MabThera® (rituximab) containing first-line regimen.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent form was read by and explained to all participants and/or their legally authorized representative. Participants signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 July 2005
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Hungary: 124
Worldwide total number of subjects	124
EEA total number of subjects	124

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)	102
From 65 to 84 years	22
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted between 08 July 2005 to 12 Aug 2013 at 15 sites in Hungary.

Pre-assignment

Screening details:

A total number of 124 patients were recruited. Of these, 83 patients completed the maintenance therapy with rituximab(MabThera) and entered the 3-year follow-up phase. Of these, 69 patients completed the follow-up phase.

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	Rituximab

Arm description:

Rituximab was administered by intravenous infusion every 8 weeks at a dose of 375 mg/m2.

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

Dosage and administration details:

All patients received 12 cycles of 375 mg/m2 of MabThera (every 8 weeks) as a treatment.

Number of subjects in period 1	Rituximab
Started	124
Completed	69
Not completed	55
Physician decision	3
Consent withdrawn by subject	5
Progression of the disease	18
Complete remission	7
Unknown	1
Non-compliance	9
Serious adverse event	6
Lost to follow-up	5
New anti-lymphoma treatment	1

Baseline characteristics

Reporting groups	
Reporting group title	Rituximab
Reporting group description:	
Rituximab was administered by intravenous infusion every 8 weeks at a dose of 375 mg/m2.	

Reporting group values	Rituximab	Total	
Number of subjects	124	124	
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)	102	102	
From 65-84 years	22	22	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	84	84	
Male	40	40	

End points

End points reporting groups

Reporting group title	Rituximab

Reporting group description:

Rituximab was administered by intravenous infusion every 8 weeks at a dose of 375 mg/m2.

Subject analysis set title	ITT (intend-to-treat) population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Patients who received at least one maintenance rituximab infusion, excluding non-eligible patients according to protocol.

Primary: Event-free survival

End point title	Event-free survival[1]

End point description:

Event-free survival (EFS) was defined as the time from baseline (Week 0) to the time to progression, relapse, death from any cause, or institution of a new treatment, whichever occurs first. Mean EFS was estimated by the Kaplan-Meier estimation and provided with their 95% confidence interval. ITT population (patients who received at least one maintenance rituximab infusion) was used for this analysis.

End point type	Primary

End point timeframe:

From randomization to the time to progression, relapse, death from any cause, or institution of a new treatment, whichever occurs first, assessed up to 5 years

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: Mean EFS was estimated by the Kaplan-Meier estimation and 95% confidence interval has been presented in the results section.

End point values	Rituximab			
Subject group type	Reporting group			
Number of subjects analysed	124			
Units: Months				
arithmetic mean (confidence interval 95%)	53.944 (50.242 to 57.647)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Adverse Events

End point title	Number of Participants With Adverse Events

End point description:

An adverse event (AE) was considered any unfavorable and unintended sign, symptom, or disease associated with the use of the study drug, whether or not considered related to the study drug. A serious adverse event (SAE) was defined as any untoward medical occurrence that is life-threatening, requires inpatient hospitalization or causes prolongation of existing hospitalization, results in persistent or significant disability/incapacity, congenital anomaly/birth defect, requires intervention to prevent permanent impairment or damage, or results in death. Safety population (participants who received at least one dose of study medication and had safety data after the first dose of study drug) was used for

this analysis.

End point type	Secondary

End point timeframe:

Up to 27 months

End point values	Rituximab			
Subject group type	Reporting group			
Number of subjects analysed	124			
Units: Participants				
SAEs	14			
Non serious AEs	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival, defined as the time between baseline (Week 0) and the date of death irrespective of the cause of death. Mean OS was estimated by the Kaplan-Meier estimation and provided with their 95% confidence interval. ITT population was used for this analysis.

End point type	Secondary

End point timeframe:

From randomization until death, assessed up to 5 years

End point values	Rituximab			
Subject group type	Reporting group			
Number of subjects analysed	124			
Units: Months				
arithmetic mean (confidence interval 95%)	72.959 (70.303 to 75.616)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to progression

End point title	Time to progression

End point description:

Time to progression (TTP) defined as time from baseline to disease progression or relapse, death from the follicular lymphoma or institution of a new regimen because of the follicular lymphoma. Mean TTP was estimated by the Kaplan-Meier estimation and provided with their 95% confidence interval. ITT population was used for this analysis.

End point type	Secondary

End point timeframe:

From baseline (Week 0) to disease progression, relapse, death from the follicular lymphoma or institution of a new regimen, whichever occurs first, assessed up to 5 years

End point values	Rituximab			
Subject group type	Reporting group			
Number of subjects analysed	124			
Units: Months				
arithmetic mean (confidence interval 95%)	56.024 (52.532 to 59.516)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to new anti-lymphoma treatment

End point title	Time to new anti-lymphoma treatment

End point description:

Time to next anti-lymphoma treatment (TTNLT) defined as time from baseline to institution of a new antilymphoma regimen (including chemo, radio or immunotherapies). Mean TTNLT was estimated by the Kaplan-Meier estimation and provided with their 95% confidence interval. ITT population was used for this analysis.

End point type	Secondary

End point timeframe:

From baseline (Week 0) to institution of a new antilymphoma regimen, assessed up to 5 years

End point values	Rituximab			
Subject group type	Reporting group			
Number of subjects analysed	124			
Units: Months				
arithmetic mean (confidence interval 95%)	59.236 (56.318 to 62.153)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response

End point title	Duration of response

End point description:

Duration of Response (DR) defined as time from first documented response to induction treatment to relapse or progression or death from the follicular lymphoma. Mean DR was estimated by the Kaplan-Meier estimation and provided with their 95% confidence interval. ITT population was used for this analysis.

End point type	Secondary

End point timeframe:

From first documented response to induction treatment to relapse or progression or death, assessed up to 5 years

End point values	Rituximab			
Subject group type	Reporting group			
Number of subjects analysed	124			
Units: Months				
arithmetic mean (confidence interval 95%)	63.159 (59.29 to 67.029)			

Statistical analyses

No statistical analyses for this end point

Secondary: Disease-free survival

End point title	Disease-free survival

End point description:

Disease-free survival (DFS) being defined as time from first documented complete response to induction treatment to relapse or progression or death from the follicular lymphoma. Mean DFS was estimated by the Kaplan-Meier estimation and provided with their 95% confidence interval. ITT population was used for this analysis.

End point type	Secondary

End point timeframe:

From first documented complete response to induction treatment to relapse or progression or death, whichever occurs first, assessed up to 5 years

End point values	Rituximab			
Subject group type	Reporting group			
Number of subjects analysed	124			
Units: Months				
arithmetic mean (confidence interval 95%)	66.737 (63.808 to 69.666)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to 3 months after last study drug administration	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups	
Reporting group title	Rituximab
Reporting group description:	
Rituximab was administered by intravenous infusion every 8 weeks at a dose of 375 mg/m2.	

Serious adverse events	Rituximab		
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 124 (11.29%)		
number of deaths (all causes)	7		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Carcinoid tumour of the gastrointestinal tract			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ovarian cancer			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Diffuse large Bcell lymphoma			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung neoplasm malignant			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Pleural neoplasm			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Generalised tonic-clonic seizure			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Vascular encephalopathy			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Blood and lymphatic system disorders			
Agranulocytosis			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Oedema			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal discomfort			

subjects affected / exposed	1 / 124 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	1 / 124 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastric ulcer				
subjects affected / exposed	1 / 124 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oral disorder				
subjects affected / exposed	1 / 124 (0.81%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Chronic obstructive pulmonary disease				
subjects affected / exposed	1 / 124 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	2 / 124 (1.61%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Psychiatric disorders				
Confusional state				
subjects affected / exposed	1 / 124 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Infections and infestations				
Acute hepatitis B				

subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Erysipelas			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatitis B			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Nasopharyngitis			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Otitis media			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Strongyloidiasis			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Rituximab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 124 (2.42%)		
Endocrine disorders			
Diabetes mellitus			
subjects affected / exposed	3 / 124 (2.42%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 March 2007	Additional requirements were added regarding the eligibility screening process. The number of sites were modified to 18. Urine pregnancy test was added to the required assessment during the maintenance therapy cycle. Appendix I was added to the protocol (Calculation of FLIPI score). Appendix J was added to the protocol (Eligibility fax form).
20 January 2010	Interim analysis was added to the protocol. Time of publication of the IA was clarified.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported