Clinical trial results:
Multicentre, Non-Randomised, Open-Label Phase II Study to Evaluate the Efficacy and Safety of Induction Treatment With Rituximab, Fludarabine, Cyclophosphamide, Followed by Rituximab Maintenance Therapy (R-Fc-Rm) in the First Lline Treatment of Chronic Lymphocytic Leukaemia

Summary

EudraCT number	2007-002733-36
Trial protocol	ES
Global end of trial date	20 May 2016

Results information

Result version number	v1 (current)
This version publication date	31 May 2017
First version publication date	31 May 2017

Trial information

Trial identification

Sponsor protocol code	ML21135

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00545714
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche AG, Roche Trial Information Hotline, 41 61 6878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, Roche Trial Information Hotline, 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	28 November 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 May 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This single arm study assessed the efficacy and safety of rituximab in combination with fludarabine and cyclophosphamide, followed by rituximab maintenance therapy, as first line treatment of participants with chronic lymphocytic leukemia (CLL).

Protection of trial subjects:

Investigators ensured that this study was conducted in full compliance with the principles of the last version of the Declaration of Helsinki and with the law and regulations of the country where the research was conducted, whichever provided greater protection to the study participants. The study fully complied with the principles stated in the "Good Clinical Practice Standards" of the International Council for Harmonisation (ICH) Tripartite Guideline (January 1997) and with all local regulations on clinical trials (Directive 2001/20/EC of the European Union and RD 223/2004).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 November 2007
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	46 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 86
Worldwide total number of subjects	86
EEA total number of subjects	86

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)	69
From 65 to 84 years	17
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Of the 86 participants treated, demographic data were available for only 84 participants, and therefore, the 2 remaining participants have been counted under 'Adults (18-64 years)' in the preceding table.

Pre-assignment

Screening details:

A total of 86 participants were enrolled in 29 centers in Spain in this two-phase study (Induction Phase and Maintenance Phase).

Period 1

Period 1 title	Induction Phase (6 Months)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Rituximab + Fludarabine + Cyclophosphamide

Arm description:

Participants received rituximab 375 milligrams per square meter (mg/m^2) as intravenous (IV) infusion on Day 0 of Cycle 1 and 500 mg/m^2 as IV infusion on Day 1 of Cycles 2-6 (cycle length = 28 days); fludarabine 25 mg/m^2 on Days 1-3 of each cycle; and cyclophosphamide 250 mg/m^2 on Days 1-3 of each cycle during the induction phase. Participants with a partial response (PR) or complete response (CR) and appropriate neutrophil conditions received maintenance treatment with rituximab (375 mg/m^2 as IV infusion every 2 months) from 3 months after Day 1 Cycle 6 up to a total of 18 doses or up to 3 years after Cycle 6 of Induction Phase.

Arm type	Experimental
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	MabThera
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received rituximab 375 mg/m^2 on Day 0 of Cycle 1 and 500 mg/m^2 on Day 1 of Cycles 2-6 (cycle length = 28 days) as IV infusion during the Induction Phase. Participants with PR or CR and appropriate neutrophil conditions received maintenance treatment with rituximab (375 mg/m^2 as IV infusion every 2 months) from 3 months after Day 1 Cycle 6 up to a total of 18 doses or up to 3 years after Cycle 6 of induction phase.

Number of subjects in period 1	Rituximab + Fludarabine + Cyclophosphamide
Started	86
Safety Population	86
Intent-to-Treat (ITT) Population	84
Completed	74
Not completed	12
Physician decision	3
Unacceptable Toxicity	6

Eligibility Criteria Violation	2
Disease Progression	1

Period 2	
Period 2 title	Maintenance Phase (36 Months)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Rituximab + Fludarabine + Cyclophosphamide

Arm description:

Participants received rituximab 375 mg/m^2 as IV infusion on Day 0 of cycle 1, and 500 mg/m^2 as IV infusion on Day 1 of cycles 2-6 (1 cycle = 28 days); fludarabine 25 mg/m^2 on Days 1 to 3 of each cycle and cyclophosphamide 250 mg/m^2 on Days 1 to 3 of each cycle during the induction phase. Participants with a partial or complete response (and appropriate neutrophil conditions) received maintenance treatment with rituximab (375 mg/m^2 as IV infusion every 2 months) from 3 months after Day 1 Cycle 6 up to a total of 18 doses or up to 3 years after Cycle 6 of induction phase.

Arm type	Experimental
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	MabThera
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received rituximab 375 mg/m^2 on Day 0 of Cycle 1 and 500 mg/m^2 on Day 1 of Cycles 2-6 (cycle length = 28 days) as IV infusion during the Induction Phase. Participants with PR or CR and appropriate neutrophil conditions received maintenance treatment with rituximab (375 mg/m^2 as IV infusion every 2 months) from 3 months after Day 1 Cycle 6 up to a total of 18 doses or up to 3 years after Cycle 6 of induction phase.

Number of subjects in period 2	Rituximab + Fludarabine + Cyclophosphamide
Started	74
Completed	42
Not completed	32
Physician decision	1
Death	2
Unacceptable Toxicity	16
Withdrawal by Subject	3
Disease Progression	9

Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	Induction Phase (6 Months)

Reporting group description:

Participants received rituximab 375 mg/m^2 as IV infusion on Day 0 of Cycle 1 and 500 mg/m^2 as IV infusion on Day 1 of Cycles 2-6 (cycle length = 28 days); fludarabine 25 mg/m^2 on Days 1-3 of each cycle; and cyclophosphamide 250 mg/m^2 on Days 1-3 of each cycle during the induction phase. Participants with a PR or CR and appropriate neutrophil conditions received maintenance treatment with rituximab (375 mg/m^2 as IV infusion every 2 months) from 3 months after Day 1 Cycle 6 up to a total of 18 doses or up to 3 years after Cycle 6 of Induction Phase.

Reporting group values	Induction Phase (6 Months)	Total	
Number of subjects	86	86	
Age Categorical Units: Subjects			

Age Continuous			
Age data were available for 84 out of 86 participants.			
Units: years			
arithmetic mean	57.92		
standard deviation	± 7.87	-	
Gender Categorical Units: Subjects			
Female	27	27	
Male	57	57	
Missing	2	2	

End points

End points reporting groups

Reporting group title	Rituximab + Fludarabine + Cyclophosphamide

Reporting group description:

Participants received rituximab 375 milligrams per square meter (mg/m^2) as intravenous (IV) infusion on Day 0 of Cycle 1 and 500 mg/m^2 as IV infusion on Day 1 of Cycles 2-6 (cycle length = 28 days); fludarabine 25 mg/m^2 on Days 1-3 of each cycle; and cyclophosphamide 250 mg/m^2 on Days 1-3 of each cycle during the induction phase. Participants with a partial response (PR) or complete response (CR) and appropriate neutrophil conditions received maintenance treatment with rituximab (375 mg/m^2 as IV infusion every 2 months) from 3 months after Day 1 Cycle 6 up to a total of 18 doses or up to 3 years after Cycle 6 of Induction Phase.

Reporting group title	Rituximab + Fludarabine + Cyclophosphamide

Reporting group description:

Participants received rituximab 375 mg/m^2 as IV infusion on Day 0 of cycle 1, and 500 mg/m^2 as IV infusion on Day 1 of cycles 2-6 (1 cycle = 28 days); fludarabine 25 mg/m^2 on Days 1 to 3 of each cycle and cyclophosphamide 250 mg/m^2 on Days 1 to 3 of each cycle during the induction phase. Participants with a partial or complete response (and appropriate neutrophil conditions) received maintenance treatment with rituximab (375 mg/m^2 as IV infusion every 2 months) from 3 months after Day 1 Cycle 6 up to a total of 18 doses or up to 3 years after Cycle 6 of induction phase.

Subject analysis set title	Rituximab + Fludarabine + Cyclophosphamide
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Participants received rituximab 375 mg/m^2 as IV infusion on Day 0 of Cycle 1 and 500 mg/m^2 as IV infusion on Day 1 of Cycles 2-6 (cycle length = 28 days); fludarabine 25 mg/m^2 on Days 1-3 of each cycle; and cyclophosphamide 250 mg/m^2 on Days 1-3 of each cycle during the induction phase. Participants with a PR or CR and appropriate neutrophil conditions received maintenance treatment with rituximab (375 mg/m^2 as IV infusion every 2 months) from 3 months after Day 1 Cycle 6 up to a total of 18 doses or up to 3 years after Cycle 6 of Induction Phase.

Subject analysis set title	Rituximab + Fludarabine + Cyclophosphamide
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants received rituximab 375 mg/m^2 as IV infusion on Day 0 of Cycle 1 and 500 mg/m^2 as IV infusion on Day 1 of Cycles 2-6 (cycle length = 28 days); fludarabine 25 mg/m^2 on Days 1-3 of each cycle; and cyclophosphamide 250 mg/m^2 on Days 1-3 of each cycle during the induction phase. Participants with a PR or CR and appropriate neutrophil conditions received maintenance treatment with rituximab (375 mg/m^2 as IV infusion every 2 months) from 3 months after Day 1 Cycle 6 up to a total of 18 doses or up to 3 years after Cycle 6 of Induction Phase.

Primary: Percentage of Participants With CR Achieved After the Rituximab, Fludarabine, and Cyclophosphamide Regimen

End point title	Percentage of Participants With CR Achieved After the Rituximab, Fludarabine, and Cyclophosphamide Regimen[1]

End point description:

CR was defined as no adenopathies (ADPs) and visceromegalies (VSMs) in physical examination (PE); no general symptoms (Sx); lymphocytes (Lymph) in peripheral blood less than (<) 4000 per cubic millimeter (mm^3); normalization of peripheral blood parameters: neutrophils (Neut) greater than (>) 1500/mm^3, platelets (Plt) >100,000/mm^3, hemoglobin (Hb) >11 grams per deciliter (g/dL) without transfusion; normocellular bone marrow (BM) with <30% Lymph; BM aspirate/biopsy with no evidence of infiltration of lymphoid nodules. ITT Population included participants who received at least one dose of study drug and met inclusion/exclusion criteria.

End point type	Primary

End point timeframe:

Month 9

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: No inferential analysis was performed. Only descriptive summaries were planned.

End point values	Rituximab + Fludarabine + Cyclophosphamide			
Subject group type	Subject analysis set			
Number of subjects analysed	84			
Units: Percentage of Participants				
number (confidence interval 95%)	95.2 (88.25 to 98.69)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Clinical Response of CR or PR as Assessed by Multiparameter Flow Cytometry

End point title	Percentage of Participants With Clinical Response of CR or PR as Assessed by Multiparameter Flow Cytometry

End point description:

CR was defined as no ADPs and VSMs in PE; no general Sx; Lymph in peripheral blood <4000/mm^3; normalization of peripheral blood parameters: Neut >1500/mm^3, Plt >100,000/mm^3, Hb >11 g/dL without transfusion; normocellular BM with <30% Lymph; BM aspirate/biopsy with no evidence of infiltration of lymphoid nodules. PR was defined as decrease >50% in Lymph in peripheral blood; reduction in ADPs >50% in total sum of up to 6 ADPs or in the baseline ADP of largest diameter (LD), no new ADP or enlargement of a prior ADP; >50% decrease in VSM; Neut >1500/mm^3 or >50% increase from Baseline; Plt >100,000/mm^3 or >50% increase from Baseline; Hb >11.0 g/dL or >50% increase from Baseline value without transfusion. Participants who met all CR criteria but had persistent anemia or thrombocytopenia were considered as PR. ITT Population.

End point type	Secondary

End point timeframe:

Post-Induction Phase (IP): at 6 months; during Maintenance Phase (MP): at Cycles 9, 12, 15, 18 (cycle length = 2 months); during Follow-Up (FU): at Follow-Up Months 6, 12, 18, 24, 30, 36

End point values	Rituximab + Fludarabine + Cyclophosphamide			
Subject group type	Subject analysis set			
Number of subjects analysed	84[2]			
Units: Percentage of Participants				
number (not applicable)				
Post-IP: CR (n= 84)	75			
Post-IP: PR (n= 84)	13.1			
MP (9 Cycles): CR (n= 47)	89.4			
MP (9 Cycles): PR (n= 47)	6.4			
MP (12 Cycles): CR (n= 33)	87.9			
MP (12 Cycles): PR (n= 33)	6.1			
MP (15 Cycles): CR (n= 22)	90.9			
MP (15 Cycles): PR (n= 22)	4.5			
MP (18 Cycles): CR (n= 59)	88.1			
MP (18 Cycles): PR (n= 59)	8.5			

6 Months FU: CR (n= 12)	83.3			
6 Months FU: PR (n= 12)	0			
12 Months FU: CR (n= 36)	94.4			
12 Months FU: PR (n= 36)	0			
18 Months FU: CR (n= 2)	100			
18 Months FU: PR (n= 2)	0			
24 Months FU: CR (n= 29)	93.1			
24 Months FU: PR (n= 29)	0			
30 Months FU: CR (n= 2)	100			
30 Months FU: PR (n= 2)	0			
36 Months FU: CR (n= 31)	100			
36 Months FU: PR (n= 31)	0			

Notes:

[2] - Here, 'n' signifies participants who were evaluable for indicated category.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Clinical Response of CR or PR Among Participants with Negative Minimal Residual Disease (MRD) as Assessed by Multiparameter Flow Cytometry

End point title	Percentage of Participants With Clinical Response of CR or PR Among Participants with Negative Minimal Residual Disease (MRD) as Assessed by Multiparameter Flow Cytometry

End point description:

CR: no ADPs and VSMs in PE; no general Sx; Lymph in peripheral blood <4000/mm^3; normalization of peripheral blood parameters: Neut >1500/mm^3, Plt >100,000/mm^3, Hb >11 g/dL without transfusion; normocellular BM with <30% Lymph; BM aspirate/biopsy with no evidence of infiltration of lymphoid nodules. PR: decrease >50% in Lymph in peripheral blood; reduction in ADPs >50% in total sum of up to 6 ADPs or in the baseline ADP of largest diameter (LD), no new ADP or enlargement of a prior ADP; >50% decrease in VSM; Neut >1500/mm^3 or >50% increase from Baseline; Plt >100,000/mm^3 or >50% increase from Baseline; Hb >11.0 g/dL or >50% increase from Baseline value without transfusion. Participants who met all CR criteria but had persistent anemia or thrombocytopenia were considered as PR. Negative MRD: Lymph <0.01% of all white blood cells (WBCs) in blood or BM after two consecutive measurements. Analysis performed only in blood during Maintenance Phase and Follow-Up.

End point type	Secondary

End point timeframe:

Post-Induction Phase: at 6 months; during Maintenance Phase: at Cycles 9, 12, 15, 18 (cycle length = 2 months); during Follow-Up: at Follow-Up Months 6, 12, 18, 24, 36

End point values	Rituximab + Fludarabine + Cyclophosphamide			
Subject group type	Subject analysis set			
Number of subjects analysed	60[3]			
Units: Percentage of Participants				
number (not applicable)				
Post-IP: Blood MRD Negative (n= 60)	100			
Post-IP: BM MRD Negative (n= 37)	100			

MP (9 Cycles): Blood MRD Negative (n= 33)	100			
MP (12 Cycles): Blood MRD Negative (n= 22)	100			
MP (15 Cycles): Blood MRD Negative (n= 16)	100			
MP (18 Cycles): Blood MRD Negative (n= 40)	100			
6 Months FU: Blood MRD Negative (n= 4)	100			
12 Months FU: Blood MRD Negative (n= 24)	100			
18 Months FU: Blood MRD Negative (n= 1)	100			
24 Months FollowFU: Blood MRD Negative (n= 19)	100			
36 Months FU: Blood MRD Negative (n= 22)	100			

Notes:

[3] - ITT Population. Those with negative MRD evaluable, where 'n' signifies those evaluable for category.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With CR With Incomplete Bone Marrow Recovery (CRi)

End point title	Percentage of Participants With CR With Incomplete Bone Marrow Recovery (CRi)

End point description:

Participants with CRi were those who met all CR criteria (including BM examinations) but had persistent anemia, thrombocytopenia, or neutropenia apparently unrelated to chronic lymphocytic leukemia (CLL) but related to drug toxicity. CR: no ADPs and VSMs in PE; no general Sx; Lymph in peripheral blood <4000/mm^3; normalization of peripheral blood parameters: Neut >1500/mm^3, Plt >100,000/mm^3, Hb >11 g/dL without transfusion; normocellular BM with <30% Lymph; BM aspirate/biopsy with no evidence of infiltration of lymphoid nodules. ITT Population.

End point type	Secondary

End point timeframe:

Baseline up to progressive disease (PD) or death due to any cause, whichever occurred first (up to 92 months)

End point values	Rituximab + Fludarabine + Cyclophosphamide			
Subject group type	Subject analysis set			
Number of subjects analysed	84			
Units: Percentage of Participants				
number (not applicable)	7.1			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as time from treatment start to death of the participant. For all other participants, the last follow-up available was taken as the last control. If the participant had not completed the study, the date of the last visit available was considered. OS was estimated using Kaplan-Meier (KM) methodology. ITT Population.

End point type	Secondary

End point timeframe:

Baseline up to death due to any cause (up to 92 months)

End point values	Rituximab + Fludarabine + Cyclophosphamide			
Subject group type	Subject analysis set			
Number of subjects analysed	84[4]			
Units: Years				
median (confidence interval 95%)	7.51 (7.5 to 99999)			

Notes:

[4] - 99999 = upper limit not estimable due to high number of censored participants.

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 was defined as time from start of study treatment to PD or death, whichever occurred first. For other participants, last follow-up available was taken as last control. If participant did not complete study, date of last visit available was considered. PFS was estimated using KM methodology. PD was defined as new ADPs (1.5 centimeters [cm]), hepato-/splenomegaly (HSM), Richter syndrome (RS), or other infiltrated organs; greater than or equal to (>/=) 50% increase in size of Baseline prior ADPs or HSM in participants with PR; Lymph increase >/=50% in peripheral blood with B Lymph >/=5000/mm^3; cytopenia attributable to CLL. Progression of any cytopenia (not related to autoimmune cytopenia) reported as a 2-g/dL decrease in basal Hb, Hb <10 g/dL, >/=50% decrease in basal Plt count, or count <100,000/mm^3 at >/=3 months post-treatment was defined as PD if BM biopsy confirmed infiltration of clonal CLL cells. ITT Population.

End point type	Secondary

End point timeframe:

Baseline up to PD or death due to any cause, whichever occurred first (up to 92 months)

End point values	Rituximab + Fludarabine + Cyclophosphamide			
Subject group type	Subject analysis set			
Number of subjects analysed	84[5]			
Units: Years				
median (confidence interval 95%)	6.96 (5.72 to 99999)			

Notes:

[5] - 99999 = upper limit not estimable due to high number of censored participants.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Died

End point title	Percentage of Participants Who Died

End point description:

Safety Population included all participants who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Baseline up to death due to any cause (up to 92 months)

End point values	Rituximab + Fludarabine + Cyclophosphamide			
Subject group type	Subject analysis set			
Number of subjects analysed	86			
Units: Percentage of Participants				
number (not applicable)	23.2			

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment-Free Survival (TFS)

End point title	Treatment-Free Survival (TFS)

End point description:

TFS was defined time from start of study treatment until participant received new chemotherapy/immunotherapy because of PD and to reduce the disease with palliative or curative intent. PD was defined as new ADPs (1.5 cm), HSM, RS, or other infiltrated organs; >/=50% increase in size of Baseline prior ADPs or HSM in participants with PR; Lymph increase >/=50% in peripheral blood with B Lymph >/=5000/mm^3; cytopenia attributable to CLL. Progression of any cytopenia (not related to autoimmune cytopenia) reported as a 2-g/dL decrease in basal Hb, Hb <10 g/dL, >/=50% decrease in basal Plt count, or count <100,000/mm^3 at >/=3 months post-treatment was defined as PD if BM biopsy confirmed infiltration of clonal CLL cells. ITT Population. Only those who received new chemotherapy/immunotherapy, as per definitions for TFS, were included in the analysis.

End point type	Secondary

End point timeframe:

Baseline up to PD or death due to any cause, whichever occurred first (up to 92 months)

End point values	Rituximab + Fludarabine + Cyclophosphamide			
Subject group type	Subject analysis set			
Number of subjects analysed	27			
Units: Years				
median (confidence interval 95%)	4.13 (2.98 to 4.87)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

DOR: time from CR/PR to MRD/PD. PD: new ADP (1.5 cm), HSM, RS, other infiltrated organs or >/=50% increase size in those with PR; blood Lymph increase >/=50% with B Lymph >/=5000/mm^3; cytopenia due to CLL. Progression of (nonautoimmune) cytopenia: 2-g/dL decrease basal Hb, Hb <10 g/dL, >/=50% decrease basal Plt or <100,000/mm^3 at >/=3 months post-treatment was PD if clonal CLL cell infiltration on BM biopsy. CR: no ADP/VSM in PE; no general Sx; blood Lymph <4000/mm^3; Neut >1500/mm^3; Plt >100,000/mm^3; Hb >11 g/dL (no transfusion); normocellular BM with <30% Lymph; BM aspirate/biopsy with no lymphoid nodule infiltration. PR: >50% decrease blood Lymph; >50% decrease in total sum up to 6 ADPs or baseline ADP of LD, no new/enlargement of prior ADP; >50% decrease VSM; Neut >1500/mm^3 or >50% increase; Plt >100,000/mm^3 or >50% increase; Hb >11.0 g/dL or >50% increase (no transfusion). All CR criteria but persistent anemia or thrombocytopenia was PR. MRD: Lymph >0.01% of blood/BM WBCs.

End point type	Secondary

End point timeframe:

From first CR or PR up to detectable MRD or disease occurrence/PD, whichever occurred first (up to 92 months)

End point values	Rituximab + Fludarabine + Cyclophosphamide			
Subject group type	Subject analysis set			
Number of subjects analysed	80[6]			
Units: Years				
median (confidence interval 95%)	99999 (99999 to 99999)			

Notes:

[6] - ITT Population. Those with CR/PR were evaluable. 99999 = not estimable due to high number censored.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Cluster of Differentiation (CD) 38 Cells >/=30% in Peripheral Blood

End point title	Percentage of Participants With Cluster of Differentiation (CD) 38 Cells >/=30% in Peripheral Blood

End point description:

Percentages of participants with CD38 expression by >/=30% of CLL cells during the Induction Phase, Maintenance Phase, and Follow-Up were reported. ITT Population.

End point type	Secondary

End point timeframe:

Post-Induction Phase: at 6 months; during Maintenance Phase: at Cycles 9, 12, 15, 18 (cycle length = 2 months); during Follow-Up: at Follow-Up Months 6, 12, 18, 24, 30, 36

End point values	Rituximab + Fludarabine + Cyclophosphamide			
Subject group type	Subject analysis set			
Number of subjects analysed	84[7]			
Units: Percentage of Participants				
number (not applicable)				
Post-IP (n= 84)	47.6			
MP (9 Cycles) (n= 47)	44.4			
MP (12 Cycles) (n= 33)	45.5			
MP (15 Cycles) (n= 22)	47.6			
MP (18 Cycles) (n= 59)	47.4			
6 Months FU (n= 12)	66.7			
12 Months FU (n= 36)	45.7			
18 Months FU (n= 2)	100			
24 Months FU (n= 29)	41.4			
30 Months FU (n= 2)	50			
36 Months FU (n= 31)	35.5			

Notes:

[7] - Here, 'n' signifies participants who were evaluable for indicated category.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Genetic Abnormalities

End point title	Percentage of Participants With Genetic Abnormalities

End point description:

Percentages of participants with genetic abnormalities (deletion 6q, deletion 11q22-q23, deletion p53, trisomy 12, and deletion 13q14) in the course of the disease during the Induction Phase and Maintenance Phase were reported. ITT Population. Designation of 'MP (xC)' refers to number of cycles in Maintenance Phase.

End point type	Secondary

End point timeframe:

Post-Induction Phase: at 6 months; during Maintenance Phase: at Cycles 9, 12, 15, 18 (cycle length = 2 months)

End point values	Rituximab + Fludarabine + Cyclophosphamide			
Subject group type	Subject analysis set			
Number of subjects analysed	84[8]			
Units: Percentage of Participants				
number (not applicable)				
Post-IP: Deletion 6q (n=84)	3.6			
Post-IP: Deletion 11q22-q23 (n=84)	26.2			
Post-IP: Deletion p53 (n= 84)	4.8			
Post-IP: Trisomy 12 (n= 84)	15.5			
Post-IP: Deletion 13q14 (n= 84)	50			
MP (9C): Deletion 6q (n= 47)	4.3			
MP (9C): Deletion 11q22-q23 (n=47)	25.5			
MP (9C): Deletion p53 (n=47)	0			
MP (9C): Trisomy 12 (n= 47)	17			
MP (9C): Deletion 13q14 (n=47)	55.3			
MP (12C): Deletion 6q (n=33)	3			
MP (12C): Deletion 11q22-q23 (n=33)	21.2			
MP (12C): Deletion p53 (n=33)	0			
MP (12C): Trisomy 12 (n=33)	21.2			
MP (12C): Deletion 13q14 (n=33)	51.5			
MP (15C): Deletion 6q (n=22)	4.5			
MP (15C): Deletion 11q22-q23 (n=22)	31.8			
MP (15C): Deletion p53 (n=22)	0			
MP (15C): Trisomy 12 (n=22)	18.2			
MP (15C): Deletion 13q14 (n=22)	59.1			
MP (18C): Deletion 6q (n=59)	3.4			
MP (18C): Deletion 11q22-q23 (n=59)	23.7			
MP (18C): Deletion p53 (n=59)	0			
MP (18C): Trisomy 12 (n=59)	18.6			
MP (18C): Deletion 13q14 (n=59)	49.2			

Notes:

[8] - Here, 'n' signifies participants who were evaluable for indicated category.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Positive and Negative Zeta-Chain-Associated Protein Kinase 70 (ZAP-70) Expression

End point title	Percentage of Participants With Positive and Negative Zeta-Chain-Associated Protein Kinase 70 (ZAP-70) Expression

End point description:

Percentages of participants with positive and negative ZAP-70 expression during the Induction Phase,

Maintenance Phase, and Follow-Up were reported. Positive ZAP-70 was defined as ZAP-70 expression by >/=20% of CLL cells. Negative ZAP-70 was defined as ZAP-70 expression by <20% of CLL cells. ITT Population.

End point type	Secondary

End point timeframe:

Post-Induction Phase: at 6 months; during Maintenance Phase: at Cycles 9, 12, 15, 18 (cycle length = 2 months); during Follow-Up: at Follow-Up Months 6, 12, 18, 24, 30, 36

End point values	Rituximab + Fludarabine + Cyclophosphamide			
Subject group type	Subject analysis set			
Number of subjects analysed	84[9]			
Units: Percentage of Participants				
number (not applicable)				
Post-IP: Positive (n= 84)	57.3			
Post-IP: Negative (n= 84)	42.7			
MP (9 Cycles): Positive (n=47)	57.5			
MP (9 Cycles): Negative (n=47)	42.5			
MP (12 Cycles): Positive (n=33)	62.1			
MP (12 Cycles): Negative (n=33)	37.9			
MP (15 Cycles): Positive (n=22)	57.1			
MP (15 Cycles): Negative (n=22)	42.9			
MP (18 Cycles): Positive (n=59)	54.9			
MP (18 Cycles): Negative (n=59)	45.1			
6 Months FU: Positive (n=12)	63.6			
6 Months FU: Negative (n=12)	36.4			
12 Months FU: Positive (n=36)	60			
12 Months FU: Negative (n=36)	40			
18 Months FU: Positive (n=2)	100			
18 Months FU: Negative (n=2)	0			
24 Months FU: Positive (n=29)	59.3			
24 Months FU: Negative (n=29)	40.7			
30 Months FU: Positive (n=2)	100			
30 Months FU: Negative (n=2)	0			
36 Months FU: Positive (n=31)	57.1			
36 Months FU: Negative (n=31)	42.9			

Notes:

[9] - Here, 'n' signifies participants who were evaluable for indicated category.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Immunoglobulin Heavy Locus (IgH) Rearrangement

End point title	Percentage of Participants With Immunoglobulin Heavy Locus (IgH) Rearrangement

End point description:

Percentages of participants with IgH rearrangement during the Induction Phase, Maintenance Phase, and

Follow-Up were reported. ITT Population.

End point type	Secondary

End point timeframe:

Post-Induction Phase: at 6 months; during Maintenance Phase: at Cycles 9, 12, 15, 18 (cycle length = 2 months); during Follow-Up: at Follow-Up Months 6, 12, 18, 24, 30, 36

End point values	Rituximab + Fludarabine + Cyclophosphamide			
Subject group type	Subject analysis set			
Number of subjects analysed	84[10]			
Units: Percentage of Participants				
number (not applicable)				
Post-IP (n= 84)	36.2			
MP (9 Cycles) (n= 47)	37.1			
MP (12 Cycles) (n= 33)	20			
MP (15 Cycles) (n= 22)	29.4			
MP (18 Cycles) (n= 59)	33.3			
6 Months FU (n= 12)	100			
12 Months FU (n= 36)	37.9			
18 Months FU (n= 2)	50			
24 Months FU (n= 29)	33.3			
30 Months FU (n= 2)	0			
36 Months FU (n= 31)	45.8			

Notes:

[10] - Here, 'n' signifies participants who were evaluable for indicated category.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With PD or Death

End point title	Percentage of Participants With PD or Death

End point description:

PD was defined as new ADPs (1.5 cm), HSM, RS, or other infiltrated organs; >/=50% increase in size of Baseline prior ADPs or HSM in participants with PR; Lymph increase >/=50% in peripheral blood with B Lymph >/=5000/mm^3; cytopenia attributable to CLL. Progression of any cytopenia (not related to autoimmune cytopenia) reported as a 2-g/dL decrease in basal Hb, Hb <10 g/dL, >/=50% decrease in basal Plt count, or count <100,000/mm^3 at >/=3 months post-treatment was defined as PD if BM biopsy confirmed infiltration of clonal CLL cells. ITT Population.

End point type	Secondary

End point timeframe:

Baseline up to PD or death due to any cause, whichever occurred first (up to 92 months)

End point values	Rituximab + Fludarabine + Cyclophosphamide			
Subject group type	Subject analysis set			
Number of subjects analysed	84			
Units: Percentage of Participants				
number (not applicable)	39.29			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline through end of Follow-Up (up to 92 months)

Adverse event reporting additional description:

Safety Population included all participants who received at least one dose of study drug.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Rituximab + Fludarabine + Cyclophosphamide

Reporting group description:

Participants received rituximab 375 mg/m^2 as IV infusion on Day 0 of Cycle 1 and 500 mg/m^2 as IV infusion on Day 1 of Cycles 2-6 (cycle length = 28 days); fludarabine 25 mg/m^2 on Days 1-3 of each cycle; and cyclophosphamide 250 mg/m^2 on Days 1-3 of each cycle during the induction phase. Participants with a PR or CR and appropriate neutrophil conditions received maintenance treatment with rituximab (375 mg/m^2 as IV infusion every 2 months) from 3 months after Day 1 Cycle 6 up to a total of 18 doses or up to 3 years after Cycle 6 of Induction Phase.

Serious adverse events	Rituximab + Fludarabine + Cyclophosphamide		
Total subjects affected by serious adverse events			
subjects affected / exposed	35 / 86 (40.70%)		
number of deaths (all causes)	20		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acoustic neuroma			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Basal cell carcinoma			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Bladder neoplasm			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Vascular disorders			
Capillary leak syndrome			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Vertebroplasty			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	6 / 86 (6.98%)		
occurrences causally related to treatment / all	5 / 7		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Cytokine release syndrome			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary sarcoidosis			

subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Jaw fracture			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	8 / 86 (9.30%)		
occurrences causally related to treatment / all	9 / 11		
deaths causally related to treatment / all	0 / 0		
Neutropenia			

subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Crohn's disease			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Malabsorption			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Pancreatitis			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic mass			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			

Renal failure			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	2 / 86 (2.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Meningitis			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pharyngitis			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	7 / 86 (8.14%)		
occurrences causally related to treatment / all	4 / 8		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection			
subjects affected / exposed	2 / 86 (2.33%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Sinusitis			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Viral myocarditis			

subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Tumour lysis syndrome			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Rituximab + Fludarabine + Cyclophosphamide		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	82 / 86 (95.35%)		
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	15 / 86 (17.44%)		
occurrences (all)	35		
Lymphopenia			
subjects affected / exposed	24 / 86 (27.91%)		
occurrences (all)	71		
Neutropenia			
subjects affected / exposed	52 / 86 (60.47%)		
occurrences (all)	203		
Thrombocytopenia			
subjects affected / exposed	18 / 86 (20.93%)		
occurrences (all)	27		
General disorders and administration site conditions			
Asthenia			

subjects affected / exposed occurrences (all) Chills subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	14 / 86 (16.28%) 23 6 / 86 (6.98%) 6 31 / 86 (36.05%) 46		
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 6 / 86 (6.98%) 8 26 / 86 (30.23%) 50 16 / 86 (18.60%) 23 15 / 86 (17.44%) 29		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	 7 / 86 (8.14%) 9		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	 5 / 86 (5.81%) 5		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	 5 / 86 (5.81%) 5		
Infections and infestations Nasopharyngitis			

subjects affected / exposed	27 / 86 (31.40%)		
occurrences (all)	47		
Pneumonia			
subjects affected / exposed	7 / 86 (8.14%)		
occurrences (all)	9		
Respiratory tract infection			
subjects affected / exposed	14 / 86 (16.28%)		
occurrences (all)	25		
Upper respiratory tract infection			
subjects affected / exposed	7 / 86 (8.14%)		
occurrences (all)	8		
Urinary tract infection			
subjects affected / exposed	8 / 86 (9.30%)		
occurrences (all)	16		

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