ClinicalTrials.gov Protocol and Results Registration System (PRS) Receipt
Release Date: 09/03/2014

CHAIROS Study A Study of MabThera/Rituxan (Rituximab) Maintenance Therapy in Patients With B-Cell Chronic Lymphocytic Leukemia (CLL) Naive to Chemotherapy

This study has been completed.

Sponsor:	Hoffmann-La Roche
Collaborators:	
Information provided by (Responsible Party):	Hoffmann-La Roche
ClinicalTrials.gov Identifier:	NCT02013817

Purpose

This study will evaluate the efficacy and safety of intense combination treatment including MabThera/Rituxan (rituximab), followed by MabThera/Rituxan maintenance therapy in patients with B-cell CLL who are naive to chemotherapy. The anticipated time on study treatment is 2.5 years.

Condition	Intervention	Phase
Lymphocytic Leukemia, Chronic	Drug: rituximab [MabThera/Rituxan] Drug: fludarabine Drug: cyclophosphamide	Phase 2

Study Type: Interventional
Study Design: Treatment, Single Group Assignment, Open Label, Non-Randomized, Safety/Efficacy Study
Official Title: CHAIROS - Effect of Early Brief Intensification by Chemoimmunotherapy With FCR Followed by FR and Rituximab Maintenance on Clinical Response in Chemo-naïve Patients With B-CLL

Further study details as provided by Hoffmann-La Roche:

Primary Outcome Measure:

- Percentage of Participants With a Best Clinical Response of Clinical Remission (CR) [Time Frame: Weeks 1, 5, 9, 12, 13, 17, 21 and 24] [Designated as safety issue: No]

Best clinical response was determined according to the National Cancer Institute (NCI) Clinical and Clinical plus (+) Radiological evaluations by central response assessment. Assessment of response was performed according to the NCI revised guidelines for the diagnosis and treatment of chronic lymphocytic lymphoma (CLL) with additional computerized tomography (CT) scan evaluation of lymphadenopathy. Per NCI guidelines, CR requires all of the following criteria at least 2 months after the last treatment: no lymphadenopathy (Ly)/ hepatomegaly/ splenomegaly/constitutional symptoms; neutrophils greater than (>)1500 per microliter (/µL), platelets (PL) >100,000/µL, hemoglobin (Hb) >11.0 grams per deciliter (g/dL), lymphocytes (LC) (less than) <4000/µL, bone marrow (BM) sample must be normocellular for age, <30% LC.

Secondary Outcome Measures:

- Percentage of Participants With the Best Clinical Response by Visit (Clinical Assessment) [Time Frame: Weeks 12 and 24 and at Final Staging (Week 4 after last maintenance dose)] [Designated as safety issue: No]
  Best clinical response was determined according to the NCI clinical evaluation and through radiological assessment. CR, CRi, CRu, partial remission (PR), partial remission with toxicity associated (PRTox), progressive disease (PD), and stable disease (SD) were evaluated. Assessment of response was performed according to the NCI revised guidelines for the diagnosis and treatment of CLL with additional CT scan evaluation of lymphadenopathy during the treatment period (Radiological). Response assessment for interim (Week 12), end of induction (Week 24) and at Final Staging (4 weeks after last maintenance dose). Last observation carried forward (LOCF) method was used for missing data. Percentages are based on the number of nonmissing observations within each stratum.
- Percentage of Participants With the Best Clinical Response by Visit (Clinical + Radiological Assessment) [Time Frame: Weeks 12 and 24 and at Final Staging (Week 4 after last maintenance dose)] [Designated as safety issue: No]
  Best clinical response was determined according to the NCI clinical evaluation and through radiological assessment. CR, CRi, CRu, PR, PRTox, PD, and SD were evaluated. Assessment of response was performed according to the NCI revised guidelines for the diagnosis and treatment of CLL with additional CT scan evaluation of lymphadenopathy during the treatment period (Radiological). Response assessment for interim (Week 12), end of induction (Week 24) and at Final Staging (4 weeks after last maintenance dose). LOCF method was used for missing data. Percentages are based on the number of nonmissing observations within each stratum.
- Time to Next Treatment - Percentage of Participants With an Event [Time Frame: Weeks 1, 5, 9, 12, 13, 17, 21 and 24 and every 8 weeks for 64 Weeks and every 6 months] [Designated as safety issue: No]
  Time to next treatment was calculated as the number of days from either discontinuation of the study drug or the administration of the last dose, until the participants needed next treatment.
- Time to Next Treatment - Time to Event [Time Frame: Weeks 1, 5, 9, 12, 13, 17, 21 and 24 and every 8 weeks for 64 Weeks and every 6 months] [Designated as safety issue: No]
  Time to next treatment was calculated as the number of days from either discontinuation of the study drug or the administration of the last dose, until the participants needed next treatment.
- Percentage of Participants With Adverse Events (AEs) [Time Frame: Day 1 of Cycles 1, 2, 3, 4, 5, and 6 to 28 days after the last trial medication.] [Designated as safety issue: No]
  AEs were recorded from the date of first medication administration until 28 days after the last trial medication.

Enrollment: 43
Study Start Date: October 2005
Primary Completion Date: September 2012
Study Completion Date: September 2012

Arms	Assigned Interventions
Experimental: MabThera/Rituxan	Drug: rituximab [MabThera/Rituxan] Every 4 weeks for 6 cycles of induction, followed by maintenance therapy every 3 months x 8

Arms	Assigned Interventions
	Drug: fludarabine Every 4 weeks, 6 cycles Drug: cyclophosphamide Every 4 weeks, 3 cycles

Eligibility

Ages Eligible for Study: 18 Years and older
Genders Eligible for Study: Both
Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:

- Adult patients, >/= 18 years of age
- B-cell CLL
- No previous chemotherapy, radiotherapy, or immunotherapy

Exclusion Criteria:

- Reduced organ function, or bone marrow dysfunction not due to CLL
- Patients with a history of other malignancies within 2 years prior to study entry, except for adequately treated cancer in situ of the cervix, or basal or squamous cell skin cancer
- Patients with a history of severe cardiac disease.

Contacts and Locations

Locations

Austria

Innsbruck, Austria, 6020
Leoben, Austria, 8700
Linz, Austria, 4020
Linz, Austria, 4020
Linz, Austria, 4010
Rankweil, Austria, 6830
Salzburg, Austria, 5020
Wels, Austria, 4600

Investigators

Study Chair: Clinical Trials Hoffmann-La Roche

More Information

Responsible Party: Hoffmann-La Roche
Study ID Numbers: ML18434
Health Authority: Austria: Federal Ministry of Health and Women

Study Results

Participant Flow

Reporting Groups

	Description
Rituximab, Fludarabine, Cyclophosphamide	Induction Phase Cycle 1 (4-week cycle): Participants received fludarabine 25 milligrams per square meter (mg/m^2) intravenously (IV) and cyclophosphamide 250 mg/m^2 IV on Days 1-3 and rituximab 375 mg/m^2 IV on Day 4. Induction Phase Cycles 2 and 3 (4-week cycles): Participants received rituximab 500 mg/m^2 IV on Day 1 and fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 1-3 Induction Phase Cycles 4 to 6 (4-week cycles): Participants received rituximab 500 mg/m^2 IV on Day 1 and fludarabine 25 mg/m^2 IV on Days 1-5. Maintenance Phase (Cycles 1-8; 12-week cycles): 8 weeks after the end of the last induction cycle, participants received maintenance therapy with rituximab 375 mg/m^2, IV once every 12 weeks for a total of 8 infusions (maximum 2 years).

Overall Study

	Rituximab, Fludarabine, Cyclophosphamide
Started	43
Completed	16
Not Completed	27
Adverse Event	12
Withdrawal by Subject	4
Death	2
Not specified	9

Baseline Characteristics

Analysis Population Description

Intent-To-Treat (ITT) population: all participants who received at least one dose of study medication.

Reporting Groups

	Description
Rituximab, Fludarabine, Cyclophosphamide	Induction Phase Cycle 1 (4-week cycle): Participants received fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 1-3 and rituximab 375 mg/m^2 IV on Day 4. Induction Phase Cycles 2 and 3 (4-week cycles): Participants received rituximab 500 mg/m^2 IV on Day 1 and fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 1-3 Induction Phase Cycles 4 to 6 (4-week cycles): Participants received rituximab 500 mg/m^2 IV on Day 1 and fludarabine 25 mg/m^2 IV on Days 1-5. Maintenance Phase (Cycles 1-8; 12-week cycles): 8 weeks after the end of the last induction cycle, participants received maintenance therapy with rituximab 375 mg/m^2, IV once every 12 weeks for a total of 8 infusions (maximum 2 years).

Baseline Measures

	Rituximab, Fludarabine, Cyclophosphamide
Number of Participants	43
Age, Continuous [units: years] Mean (Standard Deviation)	61.0 (10.1)
Gender, Male/Female [units: participants]	
Female	14
Male	29

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Percentage of Participants With a Best Clinical Response of Clinical Remission (CR)

Measure Description	Best clinical response was determined according to the National Cancer Institute (NCI) Clinical and Clinical plus (+) Radiological evaluations by central response assessment. Assessment of response was performed according to the NCI revised guidelines for the diagnosis and treatment of chronic lymphocytic lymphoma (CLL) with additional computerized tomography (CT) scan evaluation of lymphadenopathy. Per NCI guidelines, CR requires all of the following criteria at least 2 months after the last treatment: no lymphadenopathy (Ly)/ hepatomegaly/ splenomegaly/ constitutional symptoms; neutrophils greater than (>)1500 per microliter (/µL), platelets (PL) >100,000/µL, hemoglobin (Hb) >11.0 grams per deciliter (g/dL), lymphocytes (LC) (less than) <4000/µL, bone marrow (BM) sample must be normocellular for age, <30% LC.
Time Frame	Weeks 1, 5, 9, 12, 13, 17, 21 and 24
Safety Issue?	No

Analysis Population Description
ITT Population

Reporting Groups

	Description
Rituximab, Fludarabine, Cyclophosphamide	Induction Phase Cycle 1 (4-week cycle): Participants received fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 1-3 and rituximab 375 mg/m^2 IV on Day 4. Induction Phase Cycles 2 and 3 (4-week cycles): Participants received rituximab 500 mg/m^2 IV on Day 1 and fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 1-3 Induction Phase Cycles 4 to 6 (4-week cycles): Participants received rituximab 500 mg/m^2 IV on Day 1 and fludarabine 25 mg/m^2 IV on Days 1-5. Maintenance Phase (Cycles 1-8; 12-week cycles): 8 weeks after the end of the last induction cycle, participants received maintenance therapy with rituximab 375 mg/m^2, IV once every 12 weeks for a total of 8 infusions (maximum 2 years).

Measured Values

	Rituximab, Fludarabine, Cyclophosphamide
Number of Participants Analyzed	38
Percentage of Participants With a Best Clinical Response of Clinical Remission (CR) [units: percentage of participants] Number (95% Confidence Interval)	
NCI Clinical	73.7 (56.9 to 86.6)
NCI Clinical (including CRu, CRi)	94.7 (82.3 to 99.4)
NCI Clinical + Radiological	63.2 (46.0 to 78.2)
NCI Clinical + Radiological (including CRu, CRi)	78.9 (62.7 to 90.4)

2. Secondary Outcome Measure:

Measure Title	Percentage of Participants With the Best Clinical Response by Visit (Clinical Assessment)
Measure Description	Best clinical response was determined according to the NCI clinical evaluation and through radiological assessment. CR, CRi, CRu, partial remission (PR), partial remission with toxicity associated (PRTox), progressive disease (PD), and stable disease (SD) were evaluated. Assessment of response was performed according to the NCI revised guidelines for the diagnosis and treatment of CLL with additional CT scan evaluation of lymphadenopathy during the treatment period (Radiological). Response assessment for interim (Week 12), end of induction (Week 24) and at Final Staging (4 weeks after last maintenance dose). Last observation carried forward (LOCF) method was used for missing data. Percentages are based on the number of nonmissing observations within each stratum.
Time Frame	Weeks 12 and 24 and at Final Staging (Week 4 after last maintenance dose)
Safety Issue?	No

Analysis Population Description

ITT Population

Reporting Groups

	Description
Rituximab, Fludarabine, Cyclophosphamide	Induction Phase Cycle 1 (4-week cycle): Participants received fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 1-3 and rituximab 375 mg/m^2 IV on Day 4. Induction Phase Cycles 2 and 3 (4-week cycles): Participants received rituximab 500 mg/m^2 IV on Day 1 and fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 1-3 Induction Phase Cycles 4 to 6 (4-week cycles): Participants received rituximab 500 mg/m^2 IV on Day 1 and fludarabine 25 mg/m^2 IV on Days 1-5. Maintenance Phase (Cycles 1-8; 12-week cycles): 8 weeks after the end of the last induction cycle, participants received maintenance therapy with rituximab 375 mg/m^2, IV once every 12 weeks for a total of 8 infusions (maximum 2 years).

Measured Values

	Rituximab, Fludarabine, Cyclophosphamide
Number of Participants Analyzed	43
Percentage of Participants With the Best Clinical Response by Visit (Clinical Assessment) [units: percentage of participants] Number (95% Confidence Interval)	

	Rituximab, Fludarabine, Cyclophosphamide
CR, Week 12	41.9 (27.0 to 57.9)
CRu, Week 12	16.3 (6.8 to 30.7)
CRi, Week 12	16.3 (6.8 to 30.7)
PR, Week 12	11.6 (3.9 to 25.1)
PRTox, Week 12	2.3 (0.1 to 12.3)
SD, Week 12	0.0 (0.0 to 8.2)
PD, Week 12	0.0 (0.0 to 8.2)
Not evaluable, Week 12	11.6 (3.9 to 25.1)
CR, Week 24	30.2 (17.2 to 46.1)
CRu, Week 24	11.6 (3.9 to 25.1)
CRi, Week 24	37.2 (23.0 to 53.3)
PR, Week 24	9.3 (2.6 to 22.1)
PRTox, Week 24	0.0 (0.0 to 8.2)
SD, Week 24	0.0 (0.0 to 8.2)
PD, Week 24	0.0 (0.0 to 8.2)
Not evaluable, Week 24	11.6 (3.9 to 25.1)
CR, Final staging	60.5 (44.4 to 75.0)
CRu, Final staging	7.0 (1.5 to 19.1)
CRi, Final staging	11.6 (3.9 to 25.1)
PR, Final staging	7.0 (1.5 to 19.1)
PRTox, Final staging	0.0 (0.0 to 8.2)
SD, Final staging	0.0 (0.0 to 8.2)
PD, Final staging	2.3 (0.1 to 12.3)
Not evaluable, Final staging	11.6 (3.9 to 25.1)

3. Secondary Outcome Measure:

Measure Title	Percentage of Participants With the Best Clinical Response by Visit (Clinical + Radiological Assessment)
Measure Description	Best clinical response was determined according to the NCI clinical evaluation and through radiological assessment. CR, CRi, CRu, PR, PRTox, PD, and SD were evaluated. Assessment of response was performed according to the NCI revised guidelines for the diagnosis and treatment of CLL with additional CT scan evaluation of lymphadenopathy during the treatment period (Radiological). Response assessment for interim (Week 12), end of induction (Week 24) and at Final Staging (4 weeks after last maintenance dose). LOCF method was used for missing data. Percentages are based on the number of nonmissing observations within each stratum.
Time Frame	Weeks 12 and 24 and at Final Staging (Week 4 after last maintenance dose)
Safety Issue?	No

Analysis Population Description

ITT Population

Reporting Groups

	Description
Rituximab, Fludarabine, Cyclophosphamide	Induction Phase Cycle 1 (4-week cycle): Participants received fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 1-3 and rituximab 375 mg/m^2 IV on Day 4. Induction Phase Cycles 2 and 3 (4-week cycles): Participants received rituximab 500 mg/m^2 IV on Day 1 and fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 1-3 Induction Phase Cycles 4 to 6 (4-week cycles): Participants received rituximab 500 mg/m^2 IV on Day 1 and fludarabine 25 mg/m^2 IV on Days 1-5. Maintenance Phase (Cycles 1-8; 12-week cycles): 8 weeks after the end of the last induction cycle, participants received maintenance therapy with rituximab 375 mg/m^2, IV once every 12 weeks for a total of 8 infusions (maximum 2 years).

Measured Values

	Rituximab, Fludarabine, Cyclophosphamide
Number of Participants Analyzed	43
Percentage of Participants With the Best Clinical Response by Visit (Clinical + Radiological Assessment) [units: percentage of participants] Number (95% Confidence Interval)	
CR, Week 12	30.2 (17.2 to 46.1)
CRu, Week 12	4.7 (0.6 to 15.8)
CRi, Week 12	7.0 (1.5 to 19.1)

	Rituximab, Fludarabine, Cyclophosphamide
PR, Week 12	30.2 (17.2 to 46.1)
PRTox, Week 12	9.3 (2.6 to 22.1)
SD, Week 124	7.0 (1.5 to 19.1)
PD, Week 12	0.0 (0.0 to 8.2)
Not evaluable, Week 12	11.6 (3.9 to 25.1)
CR, Week 24	23.3 (11.8 to 38.6)
CRu, Week 24	7.0 (1.5 to 19.1)
CRi, Week 24	30.2 (17.2 to 46.1)
PR, Week 24	14.0 (5.3 to 27.9)
PRTox, Week 24	7.0 (1.5 to 19.1)
SD, Week 24	7.0 (1.5 to 19.1)
PD, Week 24	0.0 (0.0 to 8.2)
Not evaluable, Week 24	11.6 (3.9 to 25.1)
CR, Final staging	48.8 (33.3 to 64.5)
CRu, Final staging	7.0 (1.5 to 19.1)
CRi, Final staging	7.0 (1.5 to 19.1)
PR, Final staging	11.6 (3.9 to 25.1)
PRTox, Final staging	2.3 (0.1 to 12.3)
SD, Final staging	2.3 (0.1 to 12.3)
PD, Final staging	9.3 (2.6 to 22.1)
Not evaluable, Final staging	11.6 (3.9 to 25.1)

4. Secondary Outcome Measure:

Measure Title	Time to Next Treatment - Percentage of Participants With an Event
Measure Description	Time to next treatment was calculated as the number of days from either discontinuation of the study drug or the administration of the last dose, until the participants needed next treatment.
Time Frame	Weeks 1, 5, 9, 12, 13, 17, 21 and 24 and every 8 weeks for 64 Weeks and every 6 months

Safety Issue?	No

Analysis Population Description
[Not Specified]

Reporting Groups

	Description
Rituximab, Fludarabine, Cyclophosphamide	Induction Phase Cycle 1 (4-week cycle): Participants received fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 1-3 and rituximab 375 mg/m^2 IV on Day 4. Induction Phase Cycles 2 and 3 (4-week cycles): Participants received rituximab 500 mg/m^2 IV on Day 1 and fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 1-3 Induction Phase Cycles 4 to 6 (4-week cycles): Participants received rituximab 500 mg/m^2 IV on Day 1 and fludarabine 25 mg/m^2 IV on Days 1-5. Maintenance Phase (Cycles 1-8; 12-week cycles): 8 weeks after the end of the last induction cycle, participants received maintenance therapy with rituximab 375 mg/m^2, IV once every 12 weeks for a total of 8 infusions (maximum 2 years).

Measured Values

	Rituximab, Fludarabine, Cyclophosphamide
Number of Participants Analyzed	43
Time to Next Treatment - Percentage of Participants With an Event [units: percentage of participants]	37.2

5. Secondary Outcome Measure:

Measure Title	Time to Next Treatment - Time to Event
Measure Description	Time to next treatment was calculated as the number of days from either discontinuation of the study drug or the administration of the last dose, until the participants needed next treatment.
Time Frame	Weeks 1, 5, 9, 12, 13, 17, 21 and 24 and every 8 weeks for 64 Weeks and every 6 months
Safety Issue?	No

Analysis Population Description
[Not Specified]

Reporting Groups

	Description
Rituximab, Fludarabine, Cyclophosphamide	Induction Phase Cycle 1 (4-week cycle): Participants received fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 1-3 and rituximab 375 mg/m^2 IV on Day 4. Induction Phase Cycles 2 and 3 (4-week cycles): Participants received rituximab 500 mg/m^2 IV on Day 1 and fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 1-3 Induction Phase Cycles 4 to 6 (4-week cycles): Participants received rituximab 500 mg/m^2 IV on Day 1 and fludarabine 25 mg/m^2 IV on Days 1-5. Maintenance Phase (Cycles 1-8; 12-week cycles): 8 weeks after the end of the last induction cycle, participants received maintenance therapy with rituximab 375 mg/m^2, IV once every 12 weeks for a total of 8 infusions (maximum 2 years).

Measured Values

	Rituximab, Fludarabine, Cyclophosphamide
Number of Participants Analyzed	43
Time to Next Treatment - Time to Event [units: days] Mean (Standard Deviation)	423.3 (398.5)

6. Secondary Outcome Measure:

Measure Title	Percentage of Participants With Adverse Events (AEs)
Measure Description	AEs were recorded from the date of first medication administration until 28 days after the last trial medication.
Time Frame	Day 1 of Cycles 1, 2, 3, 4, 5, and 6 to 28 days after the last trial medication.
Safety Issue?	No

Analysis Population Description

ITT population

Reporting Groups

	Description
Rituximab, Fludarabine, Cyclophosphamide	Induction Phase Cycle 1 (4-week cycle): Participants received fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 1-3 and rituximab 375 mg/m^2 IV on Day 4. Induction Phase Cycles 2 and 3 (4-week cycles): Participants received rituximab 500 mg/m^2 IV on Day 1 and fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 1-3 Induction Phase Cycles 4 to 6 (4-week cycles): Participants received rituximab 500 mg/m^2 IV on Day 1 and fludarabine 25 mg/m^2 IV on Days 1-5. Maintenance Phase (Cycles 1-8; 12-week cycles): 8 weeks after the end of the last induction cycle, participants received maintenance therapy with rituximab 375 mg/m^2, IV once every 12 weeks for a total of 8 infusions (maximum 2 years).

Measured Values

	Rituximab, Fludarabine, Cyclophosphamide
Number of Participants Analyzed	43
Percentage of Participants With Adverse Events (AEs) [units: percentage of participants]	
Any AE	100
Related AE	93.0
Severe AE	76.7
SAE	62.8
Pregnancy	0.0

Reported Adverse Events

Time Frame	Adverse events (AEs) were recorded from the date of first medication administration until 28 days after the last trial medication.
Additional Description	Number and percentage of subjects with at least one AE/SAE starting during study until within 28 days after the last trial medication by stem organ class and preferred term.

Reporting Groups

	Description
Rituximab, Fludarabine, Cyclophosphamide	Induction Phase Cycle 1 (4-week cycle): Participants received fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 1-3 and rituximab 375 mg/m^2 IV on Day 4. Induction Phase Cycles 2 and 3 (4-week cycles): Participants received rituximab 500 mg/m^2 IV on Day 1 and fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 1-3 Induction Phase Cycles 4 to 6 (4-week cycles): Participants received rituximab 500 mg/m^2 IV on Day 1 and fludarabine 25 mg/m^2 IV on Days 1-5. Maintenance Phase (Cycles 1-8; 12-week cycles): 8 weeks after the end of the last induction cycle, participants received maintenance therapy with rituximab 375 mg/m^2, IV once every 12 weeks for a total of 8 infusions (maximum 2 years).

Serious Adverse Events

	Rituximab, Fludarabine, Cyclophosphamide
	Affected/At Risk (%)
Total	30/43 (69.77%)
Blood and lymphatic system disorders	
Anaemia [A] *	1/43 (2.33%)
Febrile neutropenia [A] *	3/43 (6.98%)
Leukopenia [A] *	2/43 (4.65%)
Gastrointestinal disorders	
Abdominal pain [A] *	1/43 (2.33%)
Aphthous stomatitis [A] *	1/43 (2.33%)
Colonic polyp [A] *	1/43 (2.33%)
Diarrhoea [A] *	1/43 (2.33%)
Stomatitis [A] *	1/43 (2.33%)
General disorders	
Chest pain [A] *	2/43 (4.65%)
Drug intolerance [A] *	1/43 (2.33%)

	Rituximab, Fludarabine, Cyclophosphamide
	Affected/At Risk (%)
General physical health deterioration [A] *	1/43 (2.33%)
Pyrexia [A] *	5/43 (11.63%)
Hepatobiliary disorders	
Bile duct stone [A] *	1/43 (2.33%)
Immune system disorders	
Anaphylactic reaction [A] *	1/43 (2.33%)
Infections and infestations	
Bronchitis [A] *	1/43 (2.33%)
Cytomegalovirus infection [A] *	1/43 (2.33%)
Encephalitis herpes [A] *	1/43 (2.33%)
Febrile infection [A] *	1/43 (2.33%)
Pharyngitis [A] *	1/43 (2.33%)
Pneumonia [A] *	2/43 (4.65%)
Pneumonia primary atypical [A] *	1/43 (2.33%)
Postoperative infection [A] *	1/43 (2.33%)
Psoas abscess [A] *	1/43 (2.33%)
Respiratory tract infection [A] *	1/43 (2.33%)
Sepsis [A] *	1/43 (2.33%)
Tuberculosis [A] *	1/43 (2.33%)
Urninary tract infection [A] *	1/43 (2.33%)
Viral infection [A] *	1/43 (2.33%)
Injury, poisoning and procedural complications	
Extradural haematoma [A] *	1/43 (2.33%)

	Rituximab, Fludarabine, Cyclophosphamide
	Affected/At Risk (%)
Femoral neck fracture [A] *	1/43 (2.33%)
Skull fracture [A] *	1/43 (2.33%)
Investigations	
Ateriogram coronary [A] *	1/43 (2.33%)
Metabolism and nutrition disorders	
Hyperglycaemia [A] *	1/43 (2.33%)
Musculoskeletal and connective tissue disorders	
Arthralgia [A] *	1/43 (2.33%)
Back pain [A] *	1/43 (2.33%)
Osteitis [A] *	1/43 (2.33%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	
Malignant melanoma [A] *	1/43 (2.33%)
Myelodysplastic syndrome [A] *	1/43 (2.33%)
Tumour lysis syndrome [A] *	1/43 (2.33%)
Nervous system disorders	
Cerebrovascular accident [A] *	1/43 (2.33%)
Subarachnoid haemorrhage [A] *	1/43 (2.33%)
Renal and urinary disorders	
Renal colic [A] *	1/43 (2.33%)
Urinary retention [A] *	1/43 (2.33%)
Respiratory, thoracic and mediastinal disorders	
Bronchospasm [A] *	1/43 (2.33%)
Skin and subcutaneous tissue disorders	

	Rituximab, Fludarabine, Cyclophosphamide
	Affected/At Risk (%)
Actinic keratosis [A] *	1/43 (2.33%)
Drug eruption [A] *	1/43 (2.33%)
Surgical and medical procedures	
Cataract operation [A] *	1/43 (2.33%)
Prostatic operation [A] *	1/43 (2.33%)
Vascular disorders	
Capillary leak syndrome [A] *	1/43 (2.33%)

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA 9.1

Other Adverse Events
Frequency Threshold Above Which Other Adverse Events are Reported: 0%

	Rituximab, Fludarabine, Cyclophosphamide
	Affected/At Risk (%)
Total	36/43 (83.72%)
Blood and lymphatic system disorders	
Anaemia [A] *	13/43 (30.23%)
Febrile neutropenia [A] *	2/43 (4.65%)
Haemolysis [A] *	2/43 (4.65%)
Leukopenia [A] *	20/43 (46.51%)
Lymphopenia [A] *	14/43 (32.56%)
Neutropenia [A] *	23/43 (53.49%)
Pancytopenia [A] *	1/43 (2.33%)
Thrombocytopenia [A] *	18/43 (41.86%)
Cardiac disorders	

	Rituximab, Fludarabine, Cyclophosphamide
	Affected/At Risk (%)
Angina pectoris [A] *	1/43 (2.33%)
Arteriosclerosis coronary artery [A] *	1/43 (2.33%)
Palpitations [A] *	1/43 (2.33%)
Ear and labyrinth disorders	
Hypoacusis [A] *	1/43 (2.33%)
Tinnitus [A] *	1/43 (2.33%)
Vertigo [A] *	2/43 (4.65%)
Endocrine disorders	
Hyperthyroidism [A] *	1/43 (2.33%)
Hypothyroidism [A] *	1/43 (2.33%)
Eye disorders	
Visual acuity reduced [A] *	2/43 (4.65%)
Gastrointestinal disorders	
Abdominal discomfort [A] *	1/43 (2.33%)
Abdominal distension [A] *	2/43 (4.65%)
Abdominal pain [A] *	4/43 (9.3%)
Abdominal pain upper [A] *	3/43 (6.98%)
Bowel movement irregularity [A] *	1/43 (2.33%)
Constipation [A] *	4/43 (9.3%)
Diarrhoea [A] *	10/43 (23.26%)
Dyspepsia [A] *	1/43 (2.33%)
Flatulence [A] *	1/43 (2.33%)
Gastritis [A] *	2/43 (4.65%)

	Rituximab, Fludarabine, Cyclophosphamide
	Affected/At Risk (%)
Gastrooesophageal reflux disease [A] *	1/43 (2.33%)
Nausea [A] *	14/43 (32.56%)
Paraesthesia oral [A] *	1/43 (2.33%)
Proctalgia [A] *	1/43 (2.33%)
Subileus [A] *	1/43 (2.33%)
Vomiting [A] *	3/43 (6.98%)
General disorders	
Chest pain [A] *	1/43 (2.33%)
Chills [A] *	3/43 (6.98%)
Fatigue [A] *	8/43 (18.6%)
Influenza like illness [A] *	3/43 (6.98%)
Mucosal inflammation [A] *	1/43 (2.33%)
Oedema [A] *	1/43 (2.33%)
Oedema peripheral [A] *	4/43 (9.3%)
Pain [A] *	3/43 (6.98%)
Pyrexia [A] *	7/43 (16.28%)
Hepatobiliary disorders	
Hepatitis [A] *	1/43 (2.33%)
Hyperbilirubinaemia [A] *	1/43 (2.33%)
Immune system disorders	
Drug hypersensitivity [A] *	1/43 (2.33%)
Food allergy [A] *	1/43 (2.33%)

	Rituximab, Fludarabine, Cyclophosphamide
	Affected/At Risk (%)
Hypersensitivity [A] *	1/43 (2.33%)
Infections and infestations	
Bronchitis [A] *	1/43 (2.33%)
Bronchitis bacterial [A] *	1/43 (2.33%)
Febrile infection [A] *	2/43 (4.65%)
Fungal infection [A] *	2/43 (4.65%)
Fungal rash [A] *	1/43 (2.33%)
Gastroenteritis [A] *	1/43 (2.33%)
Gastrointestinal infection [A] *	1/43 (2.33%)
Herpes simplex [A] *	3/43 (6.98%)
Herpes virus infection [A] *	1/43 (2.33%)
Herpes zoster [A] *	2/43 (4.65%)
Infection [A] *	3/43 (6.98%)
Influenza [A] *	4/43 (9.3%)
Laryngitis [A] *	1/43 (2.33%)
Localised infection [A] *	1/43 (2.33%)
Lymphangitis [A] *	1/43 (2.33%)
Nasopharyngitis [A] *	8/43 (18.6%)
Omphalitis [A] *	1/43 (2.33%)
Oral candidiasis [A] *	3/43 (6.98%)
Oral fungal infection [A] *	1/43 (2.33%)
Perianal abscess [A] *	1/43 (2.33%)

	Rituximab, Fludarabine, Cyclophosphamide
	Affected/At Risk (%)
Pharyngitis [A] *	1/43 (2.33%)
Postoperative infection [A] *	1/43 (2.33%)
Respiratory tract infection [A] *	2/43 (4.65%)
Rhinitis [A] *	6/43 (13.95%)
Sinusitis [A] *	3/43 (6.98%)
Tooth abscess [A] *	1/43 (2.33%)
Urinary tract infection [A] *	4/43 (9.3%)
Viral pharyngitis [A] *	1/43 (2.33%)
Injury, poisoning and procedural complications	
Neck injury [A] *	1/43 (2.33%)
Thermal burn [A] *	1/43 (2.33%)
Thoracic vertebral fracture [A] *	1/43 (2.33%)
Investigations	
C-reactive protein increased [A] *	1/43 (2.33%)
Neutrophil count decreased [A] *	1/43 (2.33%)
Weight decreased [A] *	1/43 (2.33%)
White blood cell count decreased [A] *	1/43 (2.33%)
Metabolism and nutrition disorders	
Anorexia [A] *	1/43 (2.33%)
Hypokalaemia [A] *	2/43 (4.65%)
Iron deficiency [A] *	2/43 (4.65%)
Lactose intolerance [A] *	1/43 (2.33%)
Musculoskeletal and connective tissue disorders	

	Rituximab, Fludarabine, Cyclophosphamide
	Affected/At Risk (%)
Arthralgia [A] *	3/43 (6.98%)
Arthritis [A] *	2/43 (4.65%)
Back pain [A] *	4/43 (9.3%)
Bone pain [A] *	4/43 (9.3%)
Exostosis [A] *	1/43 (2.33%)
Intervertebral disc protrusion [A] *	1/43 (2.33%)
Muscle spasms [A] *	2/43 (4.65%)
Musculoskeletal pain [A] *	3/43 (6.98%)
Myalgia [A] *	1/43 (2.33%)
Neck pain [A] *	3/43 (6.98%)
Osteoarthritis [A] *	1/43 (2.33%)
Osteoporosis [A] *	2/43 (4.65%)
Pain in extremity [A] *	2/43 (4.65%)
Pain in jaw [A] *	1/43 (2.33%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	
Lipoma [A] *	1/43 (2.33%)
Neuroendocrine tumour [A] *	1/43 (2.33%)
Nervous system disorders	
Carotid artery stenosis [A] *	1/43 (2.33%)
Carpal tunnel syndrome [A] *	1/43 (2.33%)
Convulsions local [A] *	1/43 (2.33%)
Dizziness [A] *	2/43 (4.65%)

	Rituximab, Fludarabine, Cyclophosphamide
	Affected/At Risk (%)
Dysaesthesia [A] *	1/43 (2.33%)
Headache [A] *	2/43 (4.65%)
Neuropathy [A] *	1/43 (2.33%)
Polyneuropathy [A] *	1/43 (2.33%)
Sciatica [A] *	2/43 (4.65%)
Sensory loss [A] *	1/43 (2.33%)
Psychiatric disorders	
Burnout syndrome [A] *	1/43 (2.33%)
Depression [A] *	1/43 (2.33%)
Renal and urinary disorders	
Dysuria [A] *	1/43 (2.33%)
Micturition disorder [A] *	1/43 (2.33%)
Renal pain [A] *	1/43 (2.33%)
Urinary tract pain [A] *	1/43 (2.33%)
Reproductive system and breast disorders	
Menopausal symptoms [A] *	1/43 (2.33%)
Oedema genital [A] *	1/43 (2.33%)
Testicular pain [A] *	1/43 (2.33%)
Respiratory, thoracic and mediastinal disorders	
Cough [A] *	14/43 (32.56%)
Dysphonia [A] *	1/43 (2.33%)
Dysphonia exertional [A] *	1/43 (2.33%)
Dyspnoea [A] *	2/43 (4.65%)

	Rituximab, Fludarabine, Cyclophosphamide
	Affected/At Risk (%)
Lung disorder [A] *	1/43 (2.33%)
Pharyngolaryngeal pain [A] *	2/43 (4.65%)
Skin and subcutaneous tissue disorders	
Actinic keratosis [A] *	1/43 (2.33%)
Alopecia [A] *	1/43 (2.33%)
Dermatitis acneiform [A] *	1/43 (2.33%)
Eczema [A] *	1/43 (2.33%)
Erythema [A] *	1/43 (2.33%)
Hyperkeratosis [A] *	2/43 (4.65%)
Night sweats [A] *	1/43 (2.33%)
Pemphigoid [A] *	1/43 (2.33%)
Rash [A] *	7/43 (16.28%)
Rash maculo-papular [A] *	2/43 (4.65%)
Rash pruritic [A] *	2/43 (4.65%)
Subcutaneous nodule [A] *	1/43 (2.33%)
Urticaria [A] *	1/43 (2.33%)
Vascular disorders	
Circulatory collapse [A] *	1/43 (2.33%)
Hot flush [A] *	1/43 (2.33%)
Hypertension [A] *	3/43 (6.98%)
Hypotension [A] *	1/43 (2.33%)
Vein pain [A] *	1/43 (2.33%)

	Rituximab, Fludarabine, Cyclophosphamide
	Affected/At Risk (%)
Venous insufficiency [A] *	1/43 (2.33%)

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA 9.1

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

The Study being conducted under this Agreement is part of the Overall Study. Investigator is free to publish in reputable journals or to present at professional conferences the results of the Study, but only after the first publication or presentation that involves the Overall Study. The Sponsor may request that Confidential Information be deleted and/or the publication be postponed in order to protect the Sponsor's intellectual property rights.

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