ClinicalTrials.gov Protocol and Results Registration System (PRS) Receipt
Release Date: 08/04/2014

A Study of Induction and Maintenance Treatment With MabThera (Rituximab) in Patients With Indolent B-Cell Nonfollicular Lymphomas

This study has been completed.

Sponsor:	Hoffmann-La Roche
Collaborators:	
Information provided by (Responsible Party):	Hoffmann-La Roche
ClinicalTrials.gov Identifier:	NCT01153971

Purpose

This study will evaluate the efficacy and safety of MabThera in combination chemotherapy, followed by maintenance treatment with MabThera. The anticipated time on study treatment is 1-2 years, and the target sample size is <100 individuals.

Condition	Intervention	Phase
Non-Hodgkin's Lymphoma	Drug: rituximab	Phase 2

Study Type: Interventional
Study Design: Treatment, Single Group Assignment, Open Label, Non-Randomized, Safety/Efficacy Study
Official Title: An Open-label Study of Fludarabine and Cyclophosphamide Plus MabThera Followed by Maintenance With MabThera on Failure-free Survival in Treatment-naïve Patients With Advanced Indolent B-cell Nonfollicular Lymphoma

Further study details as provided by Hoffmann-La Roche:

Primary Outcome Measure:

- Percentage of Participants Remaining Failure-Free After 2 Years From Treatment Start Date [Time Frame: Month 28] [Designated as safety issue: No]
  Percentage of participants who at 2 years from the start of treatment remained free from documented disease progression, relapse, or death. Failure status was based on tumor evaluation performed on Month 28. Participants who did not have a tumor evaluation at Month 28 were counted as failures.

Secondary Outcome Measures:

- Percentage of Participants Achieving a Best Overall Response of CR, CRu, or PR by Study Phase [Time Frame: Baseline, Months 4, 7, 11, 16, 22, 28, 34, and 40] [Designated as safety issue: No]

  CR: complete disappearance of all symptoms/objective signs of disease (enlarged lymph nodes, hepatomegaly, splenomegaly) for at least 3 months following definitive re-evaluation at end of therapy. For initial bone marrow involvement, clearance of bone marrow documented by biopsy, normalization of blood counts with granulocytes greater than (>)1,500 per microliter (/µL), hemoglobin >12 grams per deciliter (g/dL), platelets >100,000/µL. CRu: disappearance of all symptoms and nearly all measurable lesions, but persistence of some radiologic abnormalities with normalization of all biologic abnormalities; normalization of the performance status for at least 3 months after the definite evaluation of therapy. PR: at least 50 percent (%) reduction of measurable and evaluable lymphoma involvement for at least 4 weeks without occurrence of new manifestations, normalization of blood counts. Participants without evaluation at end of induction/maintenance phase were considered nonresponders.
- Percentage of Participants Achieving a Response by Response Type and Study Phase [Time Frame: Baseline, Months 4, 7, 11, 16, 22, 28, 34, and 40] [Designated as safety issue: No]

  CR: complete disappearance of all symptoms/objective signs of disease (enlarged lymph nodes, hepatomegaly, splenomegaly) for at least 3 months following definitive re-evaluation at end of therapy. For initial bone marrow involvement, clearance of bone marrow documented by biopsy, normalization of blood counts with granulocytes greater than (>)1,500 per microliter (/µL), hemoglobin >12 grams per deciliter (g/dL), platelets >100,000/µL. CRu: disappearance of all symptoms and nearly all measurable lesions, but persistence of some radiologic abnormalities with normalization of all biologic abnormalities; normalization of the performance status for at least 3 months after the definite evaluation of therapy. PR: at least 50 percent (%) reduction of measurable and evaluable lymphoma involvement for at least 4 weeks without occurrence of new manifestations, normalization of blood counts. Participants without evaluation at end of induction/maintenance phase were considered nonresponders.
- Failure-Free Survival (FFS), Percentage of Participants Estimated to be Free of Documented Disease Progression, Relapse, or Death [Time Frame: Baseline, Months 1-8, 10-12, 14, 16, 22, 28, 34 and 40] [Designated as safety issue: No]

  FFS data were analyzed using Kaplan-Meier survival analysis. FFS was measured from the date of treatment start to the date of documented disease progression, relapse, or death from any cause. Responding participants, participants who were lost to follow up, who withdrew consent, or dropped out due to adverse events (AE) were censored at their last assessment date.
- FFS - Percentage of Participants With an Event [Time Frame: Baseline, Months 1-8, 10-12, 14, 16, 22, 28, 34 and 40] [Designated as safety issue: No]

  FFS was measured from the date of treatment start to the date of documented disease progression, relapse, or death from any cause. Responding participants, participants who were lost to follow up, who withdrew consent, or who dropped out due to AEs were censored at their last assessment date.
- FFS - Time to Event [Time Frame: Baseline, Months 1-8, 10-12, 14, 16, 22, 28, 34 and 40] [Designated as safety issue: No]

  FFS was measured from the date of treatment start to the date of documented disease progression, relapse or death from any cause. Responding participants, participants who were lost to follow up, who withdrew consent or dropped out due to AEs were censored at their last assessment date. NOTE: The mean survival time and its standard error were underestimated because the largest observation was censored and the estimation was restricted to the largest event time.
- Overall Survival (OS) - Percentage of Participants Estimated to be Alive [Time Frame: Baseline, Months 1-8, 10-12, 14, 16, 22, 28, 34 and 40] [Designated as safety issue: No]

  OS data were analyzed using Kaplan-Meier survival analysis. OS was defined as the time from first dosage of study drug to the date of death from any cause.
- OS - Percentage of Participants With an Event [Time Frame: Baseline, Months 1-8, 10-12, 14, 16, 22, 28, 34 and 40.] [Designated as safety issue: No]

  OS was defined as the time from first dosage of study drug to the date of death from any cause.
- OS - Time to Event [Time Frame: Baseline, Months 1-8, 10-12, 14, 16, 22, 28, 34 and 40.] [Designated as safety issue: No]

  Overall survival was defined as the time from first dosage of study drug to the date of death from any cause.
- Disease-Free Survival (DFS) - Percentage of Participants Estimated to be Disease-Free [Time Frame: Baseline, Months 1-8, 10-12, 14, 16, 22, 28, 34 and 40] [Designated as safety issue: No]

  DFS data were analyzed using Kaplan-Meier survival analysis. DFS was defined for all participants who achieved a complete response (CR/CRu) at month 1 after the completion of treatment of the induction phase (Month 7 of the study) and was measured from the time of CR to the date of relapse.

Participants without relapse were censored at their last assessment date. Participants who died due to tumour burden were considered in relapse. Participants who died due to any other causes were censored as of the death date.

- DFS - Percentage of Participants With an Event [Time Frame: Baseline, Months 1-8, 10-12, 14, 16, 22, 28, 34 and 40.] [Designated as safety issue: No]
  DFS was defined for all patients who achieved a complete response (CR/CRu) at month 1 after the completion of treatment of the induction phase (month 7 of the study) and was measured from the time of complete response to the date of relapse. Participants without relapse were censored at their last assessment date. Participants who died due to tumour burden were considered in relapse. Participants who died due to any other causes were censored on the death date.
- DFS - Time to Event [Time Frame: Baseline, Months 1-8, 10-12, 14, 16, 22, 28, 34 and 40.] [Designated as safety issue: No]
  DFS was defined for all participants who achieved a complete response (CR/CRu) at month 1 after the completion of treatment of the induction phase (month 7 of the study) and was measured from the time of complete response to the date of relapse. Participants without relapse were censored at their last assessment date. Participants who died due to tumour burden were considered in relapse. Participants who died due to any other causes were censored on the death date. NOTE: The mean survival time and its standard error were underestimated because the largest observation was censored and the estimation was restricted to the largest event time.
- Progression-free Survival (PFS) - Percentage of Participants Estimated to Be Progress Free [Time Frame: Baseline, Months 1-8, 10-12, 14, 16, 22, 28, 34 and 40] [Designated as safety issue: No]
  PFS data were analyzed using Kaplan-Meier survival analysis. PFS was defined as the time from treatment start to the date of documented disease progression.
- PFS - Percentage of Participants With an Event [Time Frame: Baseline, Months 1-8, 10-12, 14, 16, 22, 28, 34 and 40] [Designated as safety issue: No]
  Progression-free survival was defined as the time from the date of treatment start to the date of documented disease progression.
- PFS - Time to Event [Time Frame: Baseline, Months 1-8, 10-12, 14, 16, 22, 28, 34 and 40] [Designated as safety issue: No]
  Progression-free survival was defined as the time from treatment start to the date of documented disease progression. NOTE: The mean survival time and its standard error were underestimated because the largest observation was censored and the estimation was restricted to the largest event time.
- Duration of Response (DR) - Percentage of Participants Expected to Maintain a Response [Time Frame: Baseline, Months 1-8, 10-12, 14, 16, 22, 28, 34 and 40] [Designated as safety issue: No]
  DR data were analyzed using Kaplan-Meier survival analysis. DR was defined for all participants who achieved a response (CR, CRu and PR) at month 1 after the completion of treatment of the induction phase (Month 7 of the study) and was measured from the time of response until the date of progression or relapse. Participants without relapse or progression were censored at their last assessment date. Participants who died due to tumour were considered in progression. Participants who died for any other cause were censored to the death date.
- DR - Percentage of Participants With an Event [Time Frame: Baseline, Months 1-8, 10-12, 14, 16, 22, 28, 34 and 40] [Designated as safety issue: No]
  DR was defined for all participants who achieved a response (CR, CRu and PR) at month 1 after the completion of treatment of the induction phase (Month 7 of the study) and was measured from the time of response until the date of progression or relapse. Participants without relapse or progression were censored at their last assessment date. Participants who died due to tumour were considered in progression. Participants who died for any other cause were censored to the death date.
- DR - Time to Event [Time Frame: Baseline, Months 1-8, 10-12, 14, 16, 22, 28, 34 and 40] [Designated as safety issue: No]
  DR was defined for all participants who achieved a response (CR, CRu and PR) at month 1 after the completion of treatment of the induction phase (Month 7 of the study) and was measured from the time of response until the date of progression or relapse. Participants without relapse or progression were censored at their last assessment date. Participants who died due to tumour were considered in progression. Participants who died for any other cause were censored to the death date.

Enrollment: 47
Study Start Date: July 2005
Primary Completion Date: September 2010
Study Completion Date: September 2010

Arms	Assigned Interventions
Experimental: 1	Drug: rituximab 1 Other Names: MabThera/Rituxan

Eligibility

Ages Eligible for Study: 18 Years to 65 Years
Genders Eligible for Study: Both
Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:

- adult patients 18-65 years of age;
- previously untreated indolent nonfollicular non-Hodgkin's lymphoma;
- active disease;
- >=3 involved sites.

Exclusion Criteria:

- typical chronic lymphocytic leukemia;
- other malignancies within 3 years before study, except basal or squamous cell skin cancer or cancer in situ of the cervix;
- systemic corticosteroid use for >1 month;
- significant cardiovascular disease;
- central nervous system involvement;
- hepatitis B or C virus infection, or HIV infection.

Contacts and Locations

Locations

Italy

Alessandria, Italy, 15100
Brescia, Italy, 25123
Cuneo, Italy, 12100
Firenze, Italy, 50135
Messina, Italy, 98165
Milano, Italy, 20122
Milano, Italy, 20162
Modena, Italy, 41100
Pescara, Italy, 65100
Pescara, Italy, 65124

Reggio Calabria, Italy, 89100
Reggio Emilia, Italy, 42100
Rionero in Vulture, Italy, 85028
Roma, Italy, 00161
Torino, Italy, 10126

Investigators

Study Chair:	Clinical Trials	Hoffmann-La Roche

More Information

Responsible Party:	Hoffmann-La Roche
Study ID Numbers:	ML18324
Health Authority:	Italy: Ministry of Health

Study Results

Participant Flow

Reporting Groups

	Description
Rituximab + Fludarabine + Cyclophosphamide	Cycle 1 (28-day cycle): Participants received fludarabine 25 milligrams per square meter (mg/m^2) intravenously (IV) and cyclophosphamide 250 mg/m^2 IV on Days 1, 2, and 3 and rituximab 375 mg/m^2 IV on Day 8, followed by 20 days of rest. Cycles 2-3 and Cycle 6 (28-day cycle): Participants received rituximab 375 mg/m^2 IV on Day 1 and fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 2, 3, and 4 followed by 24 days of rest. Cycles 4-5 (28-day cycle): Participants received fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 2, 3, and 4 and rituximab 375 mg/m^2 IV on Day 14, followed by 14 days of rest. Cycles 7-10 (2-month cycle): Following 2 months rest after the completion of Cycle 6, participants with complete response (CR), unconfirmed complete response (CRu), or partial response (PR), received maintenance therapy with rituximab 375 mg/m^2 IV on Day 1, followed by 2 months rest; cycle was repeated 4 times.

Induction Phase

	Rituximab + Fludarabine + Cyclophosphamide
Started	47

	Rituximab + Fludarabine + Cyclophosphamide
Completed	44
Not Completed	3
Adverse Event	2
Withdrawal by Subject	1

Maintenance Phase

	Rituximab + Fludarabine + Cyclophosphamide
Started	44
Completed	41
Not Completed	3
Adverse Event	2
Clinical relapse	1

Follow-up

	Rituximab + Fludarabine + Cyclophosphamide
Started	41
Completed	37
Not Completed	4
Adverse Event	1
Protocol Violation	1
Disease progression	2

Baseline Characteristics

Analysis Population Description

Intent-to-Treat (ITT) population: all enrolled participants who completed at least 2 cycles of treatment.

Reporting Groups

	Description
Rituximab + Fludarabine + Cyclophosphamide	Cycle 1 (28-day cycle): Participants received fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 1, 2, and 3 and rituximab 375 mg/m^2 IV on Day 8, followed by 20 days of rest. Cycles 2-3 and Cycle 6 (28-day cycle): Participants received rituximab 375 mg/m^2 IV on Day 1 and fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 2, 3, and 4 followed by 24 days of rest. Cycles 4-5 (28-day cycle): Participants received fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 2, 3, and 4 and rituximab 375 mg/m^2 IV on Day 14, followed by 14 days of rest. Cycles 7-10 (2-month cycle): Following 2 months rest after the completion of Cycle 6, participants with CR, CRu, or PR, received maintenance therapy with rituximab 375 mg/m^2 IV on Day 1, followed by 2 months rest; cycle was repeated 4 times.

Baseline Measures

	Rituximab + Fludarabine + Cyclophosphamide
Number of Participants	46
Age, Continuous [units: years] Mean (Standard Deviation)	57.3 (8.2)
Gender, Male/Female [units: participants]	
Female	18
Male	28

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Percentage of Participants Remaining Failure-Free After 2 Years From Treatment Start Date
Measure Description	Percentage of participants who at 2 years from the start of treatment remained free from documented disease progression, relapse, or death. Failure status was based on tumor evaluation performed on Month 28. Participants who did not have a tumor evaluation at Month 28 were counted as failures.
Time Frame	Month 28
Safety Issue?	No

Analysis Population Description

ITT population

Reporting Groups

	Description
Rituximab + Fludarabine + Cyclophosphamide	Cycle 1 (28-day cycle): Participants received fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 1, 2, and 3 and rituximab 375 mg/m^2 IV on Day 8, followed by 20 days of rest. Cycles 2-3 and Cycle 6 (28-day cycle): Participants received rituximab 375 mg/m^2 IV on Day 1 and fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 2, 3, and 4 followed by 24 days of rest. Cycles 4-5 (28-day cycle): Participants received fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 2, 3, and 4 and rituximab 375 mg/m^2 IV on Day 14, followed by 14 days of rest. Cycles 7-10 (2-month cycle): Following 2 months rest after the completion of Cycle 6, participants with CR, CRu, or PR, received maintenance therapy with rituximab 375 mg/m^2 IV on Day 1, followed by 2 months rest; cycle was repeated 4 times.

Measured Values

	Rituximab + Fludarabine + Cyclophosphamide
Number of Participants Analyzed	46
Percentage of Participants Remaining Failure-Free After 2 Years From Treatment Start Date [units: percentage of participants] Number (95% Confidence Interval)	73.9 (61.22 to 86.60)

Statistical Analysis 1 for Percentage of Participants Remaining Failure-Free After 2 Years From Treatment Start Date

Statistical Analysis Overview	Comparison Groups	Rituximab + Fludarabine + Cyclophosphamide
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

2. Secondary Outcome Measure:

Measure Title	Percentage of Participants Achieving a Best Overall Response of CR, CRu, or PR by Study Phase
Measure Description	CR: complete disappearance of all symptoms/objective signs of disease (enlarged lymph nodes, hepatomegaly, splenomegaly) for at least 3 months following definitive re-evaluation at end of therapy. For initial bone marrow involvement, clearance of bone marrow documented by biopsy, normalization of blood counts with granulocytes greater than (>)1,500 per microliter (/µL), hemoglobin >12 grams per deciliter (g/dL), platelets >100,000/µL. CRu: disappearance of all symptoms and nearly all measurable lesions, but persistence of some radiologic abnormalities with normalization of all biologic abnormalities; normalization of the performance status for at least 3 months after the definite evaluation of therapy. PR: at least 50 percent (%) reduction of measurable and evaluable lymphoma involvement for at least 4 weeks without occurrence of new manifestations, normalization of blood counts. Participants without evaluation at end of induction/maintenance phase were considered nonresponders.
Time Frame	Baseline, Months 4, 7, 11, 16, 22, 28, 34, and 40
Safety Issue?	No

Analysis Population Description

ITT population

Reporting Groups

	Description
Rituximab + Fludarabine + Cyclophosphamide	Cycle 1 (28-day cycle): Participants received fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 1, 2, and 3 and rituximab 375 mg/m^2 IV on Day 8, followed by 20 days of rest. Cycles 2-3 and Cycle 6 (28-day cycle): Participants received rituximab 375 mg/m^2 IV on Day 1 and fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 2, 3, and 4 followed by 24 days of rest. Cycles 4-5 (28-day cycle): Participants received fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 2, 3, and 4 and rituximab 375 mg/m^2 IV on Day 14, followed by 14 days of rest. Cycles 7-10 (2-month cycle): Following 2 months rest after the completion of Cycle 6, participants with CR, CRu, or PR, received maintenance therapy with rituximab 375 mg/m^2 IV on Day 1, followed by 2 months rest; cycle was repeated 4 times.

Measured Values

	Rituximab + Fludarabine + Cyclophosphamide
Number of Participants Analyzed	46
Percentage of Participants Achieving a Best Overall Response of CR, CRu, or PR by Study Phase [units: percentage of participants] Number (95% Confidence Interval)	
Induction Phase	95.7 (89.76 to 100.00)

	Rituximab + Fludarabine + Cyclophosphamide
Maintenance Phase	80.4 (68.97 to 91.90)

3. Secondary Outcome Measure:

Measure Title	Percentage of Participants Achieving a Response by Response Type and Study Phase
Measure Description	CR: complete disappearance of all symptoms/objective signs of disease (enlarged lymph nodes, hepatomegaly, splenomegaly) for at least 3 months following definitive re-evaluation at end of therapy. For initial bone marrow involvement, clearance of bone marrow documented by biopsy, normalization of blood counts with granulocytes greater than (>)1,500 per microliter (/µL), hemoglobin >12 grams per deciliter (g/dL), platelets >100,000/µL. CRu: disappearance of all symptoms and nearly all measurable lesions, but persistence of some radiologic abnormalities with normalization of all biologic abnormalities; normalization of the performance status for at least 3 months after the definite evaluation of therapy. PR: at least 50 percent (%) reduction of measurable and evaluable lymphoma involvement for at least 4 weeks without occurrence of new manifestations, normalization of blood counts. Participants without evaluation at end of induction/maintenance phase were considered nonresponders.
Time Frame	Baseline, Months 4, 7, 11, 16, 22, 28, 34, and 40
Safety Issue?	No

Analysis Population Description

ITT population

Reporting Groups

	Description
Rituximab + Fludarabine + Cyclophosphamide	Cycle 1 (28-day cycle): Participants received fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 1, 2, and 3 and rituximab 375 mg/m^2 IV on Day 8, followed by 20 days of rest. Cycles 2-3 and Cycle 6 (28-day cycle): Participants received rituximab 375 mg/m^2 IV on Day 1 and fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 2, 3, and 4 followed by 24 days of rest. Cycles 4-5 (28-day cycle): Participants received fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 2, 3, and 4 and rituximab 375 mg/m^2 IV on Day 14, followed by 14 days of rest. Cycles 7-10 (2-month cycle): Following 2 months rest after the completion of Cycle 6, participants with CR, CRu, or PR, received maintenance therapy with rituximab 375 mg/m^2 IV on Day 1, followed by 2 months rest; cycle was repeated 4 times.

Measured Values

	Rituximab + Fludarabine + Cyclophosphamide
Number of Participants Analyzed	46
Percentage of Participants Achieving a Response by Response Type and Study Phase [units: percentage of participants]	
CR at end of induction phase	41.3
CR at end of maintenance phase	45.7
CR at final assessment	45.7
CRu at end of induction phase	21.7
CRu at end of maintenance phase	15.2
CRu at final assessment	19.6
PR at end of induction phase	32.6
PR at end of maintenance phase	19.6
PR at final assessment	13.0
Relapse at end of induction phase	0
Relapse at end of maintenance phase	0
Relapse at final assessment	2.2
Unknown at end of induction phase	4.3
Unknown at end of maintenance phase	19.6
Unknown at final assessment	19.6

4. Secondary Outcome Measure:

Measure Title	Failure-Free Survival (FFS), Percentage of Participants Estimated to be Free of Documented Disease Progression, Relapse, or Death
Measure Description	FFS data were analyzed using Kaplan-Meier survival analysis. FFS was measured from the date of treatment start to the date of documented disease progression, relapse, or death from any cause. Responding participants, participants who were lost to follow up, who withdrew consent, or dropped out due to adverse events (AE) were censored at their last assessment date.
Time Frame	Baseline, Months 1-8, 10-12, 14, 16, 22, 28, 34 and 40

Safety Issue?	No

Analysis Population Description
ITT population

Reporting Groups

	Description
Rituximab + Fludarabine + Cyclophosphamide	Cycle 1 (28-day cycle): Participants received fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 1, 2, and 3 and rituximab 375 mg/m^2 IV on Day 8, followed by 20 days of rest. Cycles 2-3 and Cycle 6 (28-day cycle): Participants received rituximab 375 mg/m^2 IV on Day 1 and fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 2, 3, and 4 followed by 24 days of rest. Cycles 4-5 (28-day cycle): Participants received fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 2, 3, and 4 and rituximab 375 mg/m^2 IV on Day 14, followed by 14 days of rest. Cycles 7-10 (2-month cycle): Following 2 months rest after the completion of Cycle 6, participants with CR, CRu, or PR, received maintenance therapy with rituximab 375 mg/m^2 IV on Day 1, followed by 2 months rest; cycle was repeated 4 times.

Measured Values

	Rituximab + Fludarabine + Cyclophosphamide
Number of Participants Analyzed	46
Failure-Free Survival (FFS), Percentage of Participants Estimated to be Free of Documented Disease Progression, Relapse, or Death [units: percentage of participants] Number (95% Confidence Interval)	90.12 (75.48 to 96.23)

5. Secondary Outcome Measure:

Measure Title	FFS - Percentage of Participants With an Event
Measure Description	FFS was measured from the date of treatment start to the date of documented disease progression, relapse, or death from any cause. Responding participants, participants who were lost to follow up, who withdrew consent, or who dropped out due to AEs were censored at their last assessment date.
Time Frame	Baseline, Months 1-8, 10-12, 14, 16, 22, 28, 34 and 40
Safety Issue?	No

Analysis Population Description
ITT population

Reporting Groups

	Description
Rituximab + Fludarabine + Cyclophosphamide	Cycle 1 (28-day cycle): Participants received fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 1, 2, and 3 and rituximab 375 mg/m^2 IV on Day 8, followed by 20 days of rest. Cycles 2-3 and Cycle 6 (28-day cycle): Participants received rituximab 375 mg/m^2 IV on Day 1 and fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 2, 3, and 4 followed by 24 days of rest. Cycles 4-5 (28-day cycle): Participants received fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 2, 3, and 4 and rituximab 375 mg/m^2 IV on Day 14, followed by 14 days of rest. Cycles 7-10 (2-month cycle): Following 2 months rest after the completion of Cycle 6, participants with CR, CRu, or PR, received maintenance therapy with rituximab 375 mg/m^2 IV on Day 1, followed by 2 months rest; cycle was repeated 4 times.

Measured Values

	Rituximab + Fludarabine + Cyclophosphamide
Number of Participants Analyzed	46
FFS - Percentage of Participants With an Event [units: percentage of participants]	8.7

6. Secondary Outcome Measure:

Measure Title	FFS - Time to Event
Measure Description	FFS was measured from the date of treatment start to the date of documented disease progression, relapse or death from any cause. Responding participants, participants who were lost to follow up, who withdrew consent or dropped out due to AEs were censored at their last assessment date. NOTE: The mean survival time and its standard error were underestimated because the largest observation was censored and the estimation was restricted to the largest event time.
Time Frame	Baseline, Months 1-8, 10-12, 14, 16, 22, 28, 34 and 40
Safety Issue?	No

Analysis Population Description
ITT population

Reporting Groups

	Description
Rituximab + Fludarabine + Cyclophosphamide	Cycle 1 (28-day cycle): Participants received fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 1, 2, and 3 and rituximab 375 mg/m^2 IV on Day 8, followed by 20 days of rest. Cycles 2-3 and Cycle 6 (28-day cycle): Participants received rituximab 375 mg/m^2 IV on Day 1 and fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 2, 3, and 4 followed by 24 days of rest. Cycles 4-5 (28-day cycle): Participants received fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 2, 3, and 4 and rituximab 375 mg/m^2 IV on Day 14, followed by 14 days of rest. Cycles 7-10 (2-month cycle): Following 2 months rest after the completion of Cycle 6, participants with CR, CRu, or PR, received maintenance therapy with rituximab 375 mg/m^2 IV on Day 1, followed by 2 months rest; cycle was repeated 4 times.

Measured Values

	Rituximab + Fludarabine + Cyclophosphamide
Number of Participants Analyzed	46
FFS - Time to Event [units: months] Mean (Standard Error)	39.14 (0.70)

7. Secondary Outcome Measure:

Measure Title	Overall Survival (OS) - Percentage of Participants Estimated to be Alive
Measure Description	OS data were analyzed using Kaplan-Meier survival analysis. OS was defined as the time from first dosage of study drug to the date of death from any cause.
Time Frame	Baseline, Months 1-8, 10-12, 14, 16, 22, 28, 34 and 40
Safety Issue?	No

Analysis Population Description

ITT population

Reporting Groups

	Description
Rituximab + Fludarabine + Cyclophosphamide	Cycle 1 (28-day cycle): Participants received fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 1, 2, and 3 and rituximab 375 mg/m^2 IV on Day 8, followed by 20 days of rest. Cycles 2-3 and Cycle 6 (28-day cycle): Participants received rituximab 375 mg/m^2 IV on Day 1 and fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 2, 3, and 4 followed by 24 days of rest. Cycles 4-5 (28-day cycle): Participants received fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 2, 3, and 4 and rituximab 375 mg/m^2 IV on Day 14, followed by 14 days of rest. Cycles 7-10 (2-month cycle): Following 2 months rest after the completion of Cycle 6, participants with CR, CRu, or PR, received maintenance therapy with rituximab 375 mg/m^2 IV on Day 1, followed by 2 months rest; cycle was repeated 4 times.

Measured Values

	Rituximab + Fludarabine + Cyclophosphamide
Number of Participants Analyzed	46
Overall Survival (OS) - Percentage of Participants Estimated to be Alive [units: percentage of participants] Number (95% Confidence Interval)	97.44 (83.16 to 99.64)

8. Secondary Outcome Measure:

Measure Title	OS - Percentage of Participants With an Event
Measure Description	OS was defined as the time from first dosage of study drug to the date of death from any cause.
Time Frame	Baseline, Months 1-8, 10-12, 14, 16, 22, 28, 34 and 40.
Safety Issue?	No

Analysis Population Description

ITT population

Reporting Groups

	Description
Rituximab + Fludarabine + Cyclophosphamide	Cycle 1 (28-day cycle): Participants received fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 1, 2, and 3 and rituximab 375 mg/m^2 IV on Day 8, followed by 20 days of rest. Cycles 2-3 and Cycle 6 (28-day cycle): Participants received rituximab 375 mg/m^2 IV on Day 1 and fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 2, 3, and 4 followed by 24 days of rest. Cycles 4-5 (28-day cycle): Participants received fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 2, 3, and 4 and rituximab 375 mg/m^2 IV on Day 14, followed by 14 days of rest. Cycles 7-10 (2-month cycle): Following 2 months rest after the completion of Cycle 6, participants with CR, CRu, or PR, received maintenance therapy with rituximab 375 mg/m^2 IV on Day 1, followed by 2 months rest; cycle was repeated 4 times.

Measured Values

	Rituximab + Fludarabine + Cyclophosphamide
Number of Participants Analyzed	46
OS - Percentage of Participants With an Event [units: percentage of participants]	2.17

9. Secondary Outcome Measure:

Measure Title	OS - Time to Event
Measure Description	Overall survival was defined as the time from first dosage of study drug to the date of death from any cause.
Time Frame	Baseline, Months 1-8, 10-12, 14, 16, 22, 28, 34 and 40.
Safety Issue?	No

Analysis Population Description

ITT population

Reporting Groups

	Description
Rituximab + Fludarabine + Cyclophosphamide	Cycle 1 (28-day cycle): Participants received fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 1, 2, and 3 and rituximab 375 mg/m^2 IV on Day 8, followed by 20 days of rest. Cycles 2-3 and Cycle 6 (28-day cycle): Participants received rituximab 375 mg/m^2 IV on Day 1 and fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 2, 3, and 4 followed by 24 days of rest. Cycles 4-5 (28-day cycle): Participants received fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 2, 3, and 4 and rituximab 375 mg/m^2 IV on Day 14, followed by 14 days of rest. Cycles 7-10 (2-month cycle): Following 2 months rest after the completion of Cycle 6, participants with CR, CRu, or PR, received maintenance therapy with rituximab 375 mg/m^2 IV on Day 1, followed by 2 months rest; cycle was repeated 4 times.

Measured Values

	Rituximab + Fludarabine + Cyclophosphamide
Number of Participants Analyzed	46
OS - Time to Event [units: months] Mean (Standard Error)	38.6 (NA) [1]

[1] Standard error could not be determined because the largest observation was censored and the estimation was restricted to the largest event time.

10. Secondary Outcome Measure:

Measure Title	Disease-Free Survival (DFS) - Percentage of Participants Estimated to be Disease-Free
Measure Description	DFS data were analyzed using Kaplan-Meier survival analysis. DFS was defined for all participants who achieved a complete response (CR/CRu) at month 1 after the completion of treatment of the induction phase (Month 7 of the study) and was measured from the time of CR to the date of relapse. Participants without relapse were censored at their last assessment date. Participants who died due to tumour burden were considered in relapse. Participants who died due to any other causes were censored as of the death date.
Time Frame	Baseline, Months 1-8, 10-12, 14, 16, 22, 28, 34 and 40
Safety Issue?	No

Analysis Population Description

ITT population; only participants who achieved a complete response (CR/CRu) at month 1 after the completion of treatment of the induction phase were included in the analysis.

Reporting Groups

	Description
Rituximab + Fludarabine + Cyclophosphamide	Cycle 1 (28-day cycle): Participants received fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 1, 2, and 3 and rituximab 375 mg/m^2 IV on Day 8, followed by 20 days of rest. Cycles 2-3 and Cycle 6 (28-day cycle): Participants received rituximab 375 mg/m^2 IV on Day 1 and fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 2, 3, and 4 followed by 24 days of rest. Cycles 4-5 (28-day cycle): Participants received fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 2, 3, and 4 and rituximab 375 mg/m^2 IV on Day 14, followed by 14 days of rest. Cycles 7-10 (2-month cycle): Following 2 months rest after the completion of Cycle 6, participants with CR, CRu, or PR, received maintenance therapy with rituximab 375 mg/m^2 IV on Day 1, followed by 2 months rest; cycle was repeated 4 times.

Measured Values

	Rituximab + Fludarabine + Cyclophosphamide
Number of Participants Analyzed	29
Disease-Free Survival (DFS) - Percentage of Participants Estimated to be Disease-Free [units: percentage of participants] Number (95% Confidence Interval)	87.70 (65.84 to 95.96)

11. Secondary Outcome Measure:

Measure Title	DFS - Percentage of Participants With an Event
Measure Description	DFS was defined for all patients who achieved a complete response (CR/CRu) at month 1 after the completion of treatment of the induction phase (month 7 of the study) and was measured from the time of complete response to the date of relapse. Participants without relapse were censored at their last assessment date. Participants who died due to tumour burden were considered in relapse. Participants who died due to any other causes were censored on the death date.
Time Frame	Baseline, Months 1-8, 10-12, 14, 16, 22, 28, 34 and 40.
Safety Issue?	No

Analysis Population Description

ITT population; only participants who achieved a complete response (CR/CRu) at month 1 after the completion of treatment of the induction phase were included in the analysis.

Reporting Groups

	Description
Rituximab + Fludarabine + Cyclophosphamide	Cycle 1 (28-day cycle): Participants received fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 1, 2, and 3 and rituximab 375 mg/m^2 IV on Day 8, followed by 20 days of rest. Cycles 2-3 and Cycle 6 (28-day cycle): Participants received rituximab 375 mg/m^2 IV on Day 1 and fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 2, 3, and 4 followed by 24 days of rest. Cycles 4-5 (28-day cycle): Participants received fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 2, 3, and 4 and rituximab 375 mg/m^2 IV on Day 14, followed by 14 days of rest. Cycles 7-10 (2-month cycle): Following 2 months rest after the completion of Cycle 6, participants with CR, CRu, or PR, received maintenance therapy with rituximab 375 mg/m^2 IV on Day 1, followed by 2 months rest; cycle was repeated 4 times.

Measured Values

	Rituximab + Fludarabine + Cyclophosphamide
Number of Participants Analyzed	29
DFS - Percentage of Participants With an Event [units: percentage of participants]	10.34

12. Secondary Outcome Measure:

Measure Title	DFS - Time to Event
Measure Description	DFS was defined for all participants who achieved a complete response (CR/CRu) at month 1 after the completion of treatment of the induction phase (month 7 of the study) and was measured from the time of complete response to the date of relapse. Participants without relapse were censored at their last assessment date. Participants who died due to tumour burden were considered in relapse. Participants who died due to any other causes were censored on the death date. NOTE: The mean survival time and its standard error were underestimated because the largest observation was censored and the estimation was restricted to the largest event time.
Time Frame	Baseline, Months 1-8, 10-12, 14, 16, 22, 28, 34 and 40.
Safety Issue?	No

Analysis Population Description

ITT population; only participants who achieved a complete response (CR/CRu) at month 1 after the completion of treatment of the induction phase were included in the analysis.

Reporting Groups

	Description
Rituximab + Fludarabine + Cyclophosphamide	Cycle 1 (28-day cycle): Participants received fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 1, 2, and 3 and rituximab 375 mg/m^2 IV on Day 8, followed by 20 days of rest. Cycles 2-3 and Cycle 6 (28-day cycle): Participants received rituximab 375 mg/m^2 IV on Day 1 and fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 2, 3, and 4 followed by 24 days of rest. Cycles 4-5 (28-day cycle): Participants received fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 2, 3, and 4 and rituximab 375 mg/m^2 IV on Day 14, followed by 14 days of rest. Cycles 7-10 (2-month cycle): Following 2 months rest after the completion of Cycle 6, participants with CR, CRu, or PR, received maintenance therapy with rituximab 375 mg/m^2 IV on Day 1, followed by 2 months rest; cycle was repeated 4 times.

Measured Values

	Rituximab + Fludarabine + Cyclophosphamide
Number of Participants Analyzed	29
DFS - Time to Event [units: months] Mean (Standard Error)	32.51 (0.58)

13. Secondary Outcome Measure:

Measure Title	Progression-free Survival (PFS) - Percentage of Participants Estimated to Be Progress Free
Measure Description	PFS data were analyzed using Kaplan-Meier survival analysis. PFS was defined as the time from treatment start to the date of documented disease progression.
Time Frame	Baseline, Months 1-8, 10-12, 14, 16, 22, 28, 34 and 40
Safety Issue?	No

Analysis Population Description

ITT population

Reporting Groups

	Description
Rituximab + Fludarabine + Cyclophosphamide	Cycle 1 (28-day cycle): Participants received fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 1, 2, and 3 and rituximab 375 mg/m^2 IV on Day 8, followed by 20 days of rest. Cycles 2-3 and Cycle 6 (28-day cycle): Participants received rituximab 375 mg/m^2 IV on Day 1 and fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 2, 3, and 4 followed by 24 days of rest. Cycles 4-5 (28-day cycle): Participants received fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 2, 3, and 4 and rituximab 375 mg/m^2 IV on Day 14, followed by 14 days of rest. Cycles 7-10 (2-month cycle): Following 2 months rest after the completion of Cycle 6, participants with CR, CRu, or PR, received maintenance therapy with rituximab 375 mg/m^2 IV on Day 1, followed by 2 months rest; cycle was repeated 4 times.

Measured Values

	Rituximab + Fludarabine + Cyclophosphamide
Number of Participants Analyzed	46
Progression-free Survival (PFS) - Percentage of Participants Estimated to Be Progress Free [units: percentage of participants] Number (95% Confidence Interval)	90.12 (75.48 to 96.23)

14. Secondary Outcome Measure:

Measure Title	PFS - Percentage of Participants With an Event
Measure Description	Progression-free survival was defined as the time from the date of treatment start to the date of documented disease progression.
Time Frame	Baseline, Months 1-8, 10-12, 14, 16, 22, 28, 34 and 40
Safety Issue?	No

Analysis Population Description

ITT population

Reporting Groups

	Description
Rituximab + Fludarabine + Cyclophosphamide	Cycle 1 (28-day cycle): Participants received fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 1, 2, and 3 and rituximab 375 mg/m^2 IV on Day 8, followed by 20 days of rest. Cycles 2-3 and Cycle 6 (28-day cycle): Participants received rituximab 375 mg/m^2 IV on Day 1 and fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 2, 3, and 4 followed by 24 days of rest. Cycles 4-5 (28-day cycle): Participants received fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 2, 3, and 4 and rituximab 375 mg/m^2 IV on Day 14, followed by 14 days of rest. Cycles 7-10 (2-month cycle): Following 2 months rest after the completion of Cycle 6, participants with CR, CRu, or PR, received maintenance therapy with rituximab 375 mg/m^2 IV on Day 1, followed by 2 months rest; cycle was repeated 4 times.

Measured Values

	Rituximab + Fludarabine + Cyclophosphamide
Number of Participants Analyzed	46
PFS - Percentage of Participants With an Event [units: percentage of participants]	8.70

15. Secondary Outcome Measure:

Measure Title	PFS - Time to Event
Measure Description	Progression-free survival was defined as the time from treatment start to the date of documented disease progression. NOTE: The mean survival time and its standard error were underestimated because the largest observation was censored and the estimation was restricted to the largest event time.
Time Frame	Baseline, Months 1-8, 10-12, 14, 16, 22, 28, 34 and 40
Safety Issue?	No

Analysis Population Description

ITT population

Reporting Groups

	Description
Rituximab + Fludarabine + Cyclophosphamide	Cycle 1 (28-day cycle): Participants received fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 1, 2, and 3 and rituximab 375 mg/m^2 IV on Day 8, followed by 20 days of rest. Cycles 2-3 and Cycle 6 (28-day cycle): Participants received rituximab 375 mg/m^2 IV on Day 1 and fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 2, 3, and 4 followed by 24 days of rest. Cycles 4-5 (28-day cycle): Participants received fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 2, 3, and 4 and rituximab 375 mg/m^2 IV on Day 14, followed by 14 days of rest. Cycles 7-10 (2-month cycle): Following 2 months rest after the completion of Cycle 6, participants with CR, CRu, or PR, received maintenance therapy with rituximab 375 mg/m^2 IV on Day 1, followed by 2 months rest; cycle was repeated 4 times.

Measured Values

	Rituximab + Fludarabine + Cyclophosphamide
Number of Participants Analyzed	46
PFS - Time to Event [units: months] Mean (Standard Error)	39.14 (0.70)

16. Secondary Outcome Measure:

Measure Title	Duration of Response (DR) - Percentage of Participants Expected to Maintain a Response
Measure Description	DR data were analyzed using Kaplan-Meier survival analysis. DR was defined for all participants who achieved a response (CR, CRu and PR) at month 1 after the completion of treatment of the induction phase (Month 7 of the study) and was measured from the time of response until the date of progression or relapse. Participants without relapse or progression were censored at their last assessment date. Participants who died due to tumour were considered in progression. Participants who died for any other cause were censored to the death date.
Time Frame	Baseline, Months 1-8, 10-12, 14, 16, 22, 28, 34 and 40
Safety Issue?	No

Analysis Population Description

ITT population; only participants who achieved a response (CR, CRu and PR) at month 1 after the completion of treatment of the induction phase of the study were included in the analysis.

Reporting Groups

	Description
Rituximab + Fludarabine + Cyclophosphamide	Cycle 1 (28-day cycle): Participants received fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 1, 2, and 3 and rituximab 375 mg/m^2 IV on Day 8, followed by 20 days of rest. Cycles 2-3 and Cycle 6 (28-day cycle): Participants received rituximab 375 mg/m^2 IV on Day 1 and fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 2, 3, and 4 followed by 24 days of rest. Cycles 4-5 (28-day cycle): Participants received fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 2, 3, and 4 and rituximab 375 mg/m^2 IV on Day 14, followed by 14 days of rest. Cycles 7-10 (2-month cycle): Following 2 months rest after the completion of Cycle 6, participants with CR, CRu, or PR, received maintenance therapy with rituximab 375 mg/m^2 IV on Day 1, followed by 2 months rest; cycle was repeated 4 times.

Measured Values

	Rituximab + Fludarabine + Cyclophosphamide
Number of Participants Analyzed	44
Duration of Response (DR) - Percentage of Participants Expected to Maintain a Response [units: percentage of participants] Number (95% Confidence Interval)	90.07 (75.45 to 96.19)

17. Secondary Outcome Measure:

Measure Title	DR - Percentage of Participants With an Event
Measure Description	DR was defined for all participants who achieved a response (CR, CRu and PR) at month 1 after the completion of treatment of the induction phase (Month 7 of the study) and was measured from the time of response until the date of progression or relapse. Participants without relapse or progression were censored at their last assessment date. Participants who died due to tumour were considered in progression. Participants who died for any other cause were censored to the death date.
Time Frame	Baseline, Months 1-8, 10-12, 14, 16, 22, 28, 34 and 40
Safety Issue?	No

Analysis Population Description

ITT population; only participants who achieved a response (CR, CRu and PR) at month 1 after the completion of treatment of the induction phase of the study were included in the analysis.

Reporting Groups

	Description
Rituximab + Fludarabine + Cyclophosphamide	Cycle 1 (28-day cycle): Participants received fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 1, 2, and 3 and rituximab 375 mg/m^2 IV on Day 8, followed by 20 days of rest. Cycles 2-3 and Cycle 6 (28-day cycle): Participants received rituximab 375 mg/m^2 IV on Day 1 and fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 2, 3, and 4 followed by 24 days of rest. Cycles 4-5 (28-day cycle): Participants received fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 2, 3, and 4 and rituximab 375 mg/m^2 IV on Day 14, followed by 14 days of rest. Cycles 7-10 (2-month cycle): Following 2 months rest after the completion of Cycle 6, participants with CR, CRu, or PR, received maintenance therapy with rituximab 375 mg/m^2 IV on Day 1, followed by 2 months rest; cycle was repeated 4 times.

Measured Values

	Rituximab + Fludarabine + Cyclophosphamide
Number of Participants Analyzed	44
DR - Percentage of Participants With an Event [units: percentage of participants]	9.09

18. Secondary Outcome Measure:

Measure Title	DR - Time to Event
Measure Description	DR was defined for all participants who achieved a response (CR, CRu and PR) at month 1 after the completion of treatment of the induction phase (Month 7 of the study) and was measured from the time of response until the date of progression or relapse. Participants without relapse or progression were censored at their last assessment date. Participants who died due to tumour were considered in progression. Participants who died for any other cause were censored to the death date.
Time Frame	Baseline, Months 1-8, 10-12, 14, 16, 22, 28, 34 and 40
Safety Issue?	No

Analysis Population Description

ITT population: only participants who achieved a response (CR, CRu and PR) at month 1 after the completion of treatment of the induction phase of the study were included in the analysis.

Reporting Groups

	Description
Rituximab + Fludarabine + Cyclophosphamide	Cycle 1 (28-day cycle): Participants received fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 1, 2, and 3 and rituximab 375 mg/m^2 IV on Day 8, followed by 20 days of rest. Cycles 2-3 and Cycle 6 (28-day cycle): Participants received rituximab 375 mg/m^2 IV on Day 1 and fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 2, 3, and 4 followed by 24 days of rest. Cycles 4-5 (28-day cycle): Participants received fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 2, 3, and 4 and rituximab 375 mg/m^2 IV on Day 14, followed by 14 days of rest. Cycles 7-10 (2-month cycle): Following 2 months rest after the completion of Cycle 6, participants with CR, CRu, or PR, received maintenance therapy with rituximab 375 mg/m^2 IV on Day 1, followed by 2 months rest; cycle was repeated 4 times.

Measured Values

	Rituximab + Fludarabine + Cyclophosphamide
Number of Participants Analyzed	44
DR - Time to Event [units: months] Mean (Standard Error)	32.19 (0.72)

Reported Adverse Events

Time Frame	Treatment-emergent adverse events (AEs) were reported throughout the study (up to 40 months).
Additional Description	[Not specified]

Reporting Groups

	Description
Rituximab + Fludarabine + Cyclophosphamide	Cycle 1 (28-day cycle): Participants received fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 1, 2, and 3 and rituximab 375 mg/m^2 IV on Day 8, followed by 20 days of rest. Cycles 2-3 and Cycle 6 (28-day cycle): Participants received rituximab 375 mg/m^2 IV on Day 1 and fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 2, 3, and 4 followed by 24 days of rest. Cycles 4-5 (28-day cycle): Participants received fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV on Days 2, 3, and 4 and rituximab 375 mg/m^2 IV on Day 14, followed by 14 days of rest. Cycles 7-10 (2-month cycle): Following 2 months rest after the completion of Cycle 6, participants with CR, CRu, or PR, received maintenance therapy with rituximab 375 mg/m^2 IV on Day 1, followed by 2 months rest; cycle was repeated 4 times.

Serious Adverse Events

	Rituximab + Fludarabine + Cyclophosphamide
	Affected/At Risk (%)
Total	16/47 (34.04%)
Blood and lymphatic system disorders	
Febrile neutropenia [A] *	1/47 (2.13%)
Neutropenia [A] *	2/47 (4.26%)
Cardiac disorders	
Mitral valve incompetence [A] *	1/47 (2.13%)
Congenital, familial and genetic disorders	
Renal dysplasia [A] *	1/47 (2.13%)
General disorders	
Pyrexia [A] *	1/47 (2.13%)
Hepatobiliary disorders	
Cholecystitis [A] *	1/47 (2.13%)
Infections and infestations	
Bronchopneumonia [A] *	1/47 (2.13%)

	Rituximab + Fludarabine + Cyclophosphamide
	Affected/At Risk (%)
Pneumonia [A] *	3/47 (6.38%)
Staphylococcal infection [A] *	1/47 (2.13%)
Musculoskeletal and connective tissue disorders	
Arthralgia [A] *	1/47 (2.13%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	
Bladder cancer [A] *	1/47 (2.13%)
Neoplasm [A] *	1/47 (2.13%)
Nervous system disorders	
Neuropathy peripheral [A] *	1/47 (2.13%)
Reproductive system and breast disorders	
Benign prostatic hyperplasia [A] *	1/47 (2.13%)
Respiratory, thoracic and mediastinal disorders	
Pleural effusion [A] *	1/47 (2.13%)

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA (10.1)

Other Adverse Events

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

	Rituximab + Fludarabine + Cyclophosphamide
	Affected/At Risk (%)
Total	47/47 (100%)
Blood and lymphatic system disorders	
Anaemia [A] *	8/47 (17.02%)
Febrile neutropenia [A] *	1/47 (2.13%)
Leukopenia [A] *	18/47 (38.3%)

	Rituximab + Fludarabine + Cyclophosphamide
	Affected/At Risk (%)
Neutropenia [A] *	29/47 (61.7%)
Pancytopenia [A] *	2/47 (4.26%)
Thrombocytopenia [A] *	1/47 (2.13%)
Cardiac disorders	
Pericardial effusion [A] *	1/47 (2.13%)
Congenital, familial and genetic disorders	
Hydrocele [A] *	2/47 (4.26%)
Ear and labyrinth disorders	
Ear pain [A] *	1/47 (2.13%)
Vertigo [A] *	1/47 (2.13%)
Eye disorders	
Conjunctivitis [A] *	1/47 (2.13%)
Dry eye [A] *	1/47 (2.13%)
Visual disturbance [A] *	1/47 (2.13%)
Gastrointestinal disorders	
Abdominal distension [A] *	1/47 (2.13%)
Abdominal pain upper [A] *	2/47 (4.26%)
Colitis [A] *	1/47 (2.13%)
Constipation [A] *	1/47 (2.13%)
Diarrhoea [A] *	5/47 (10.64%)
Dysphagia [A] *	1/47 (2.13%)
Enteritis [A] *	1/47 (2.13%)
Gastritis [A] *	2/47 (4.26%)

	Rituximab + Fludarabine + Cyclophosphamide
	Affected/At Risk (%)
Nausea [A] *	20/47 (42.55%)
Stomatitis [A] *	10/47 (21.28%)
Vomiting [A] *	5/47 (10.64%)
General disorders	
Asthenia [A] *	16/47 (34.04%)
Chills [A] *	2/47 (4.26%)
Fatigue [A] *	1/47 (2.13%)
Hyperthermia [A] *	1/47 (2.13%)
Mucosal inflammation [A] *	1/47 (2.13%)
Oedema [A] *	1/47 (2.13%)
Oedema peripheral [A] *	2/47 (4.26%)
Pain [A] *	4/47 (8.51%)
Pyrexia [A] *	23/47 (48.94%)
Hepatobiliary disorders	
Cholelithiasis [A] *	1/47 (2.13%)
Hepatitis [A] *	1/47 (2.13%)
Immune system disorders	
Allergy to arthropod bite [A] *	1/47 (2.13%)
Amyloidosis [A] *	1/47 (2.13%)
Hypersensitivity [A] *	1/47 (2.13%)
Hypogammaglobulinaemia [A] *	5/47 (10.64%)
Infections and infestations	
Bronchitis [A] *	6/47 (12.77%)

	Rituximab + Fludarabine + Cyclophosphamide
	Affected/At Risk (%)
Conjunctivitis infective [A] *	1/47 (2.13%)
Conjunctivitis viral [A] *	1/47 (2.13%)
Cystitis [A] *	2/47 (4.26%)
Ear infection [A] *	2/47 (4.26%)
Erythema induratum [A] *	1/47 (2.13%)
Fungal infection [A] *	1/47 (2.13%)
Haemophilus infection [A] *	1/47 (2.13%)
Herpes simplex [A] *	1/47 (2.13%)
Herpes zoster [A] *	8/47 (17.02%)
Influenza [A] *	2/47 (4.26%)
Labyrinthitis [A] *	1/47 (2.13%)
Oral candidiasis [A] *	1/47 (2.13%)
Pharyngitis [A] *	1/47 (2.13%)
Pneumonia [A] *	2/47 (4.26%)
Pulmonary mycosis [A] *	1/47 (2.13%)
Rhinitis [A] *	4/47 (8.51%)
Sinusitis [A] *	2/47 (4.26%)
Upper respiratory tract infection [A] *	1/47 (2.13%)
Urinary tract infection [A] *	2/47 (4.26%)
Injury, poisoning and procedural complications	
Contusion [A] *	1/47 (2.13%)
Investigations	

	Rituximab + Fludarabine + Cyclophosphamide
	Affected/At Risk (%)
Alanine aminotransferase increased [A] *	2/47 (4.26%)
Aspartate aminotransferase increased [A] *	2/47 (4.26%)
Beta 2 microglobulin increased [A] *	1/47 (2.13%)
Blood lactate dehydrogenase increased [A] *	1/47 (2.13%)
Gamma-glutamyltransferase increased [A] *	2/47 (4.26%)
Red blood cell sedimentation rate increased [A] *	1/47 (2.13%)
Transaminases increased [A] *	1/47 (2.13%)
Metabolism and nutrition disorders	
Anorexia [A] *	1/47 (2.13%)
Hyperglycaemia [A] *	1/47 (2.13%)
Hyperuricaemia [A] *	1/47 (2.13%)
Musculoskeletal and connective tissue disorders	
Arthralgia [A] *	5/47 (10.64%)
Arthritis [A] *	1/47 (2.13%)
Groin pain [A] *	1/47 (2.13%)
Musculoskeletal pain [A] *	1/47 (2.13%)
Myalgia [A] *	2/47 (4.26%)
Tenosynovitis [A] *	1/47 (2.13%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	
Bladder cancer [A] *	1/47 (2.13%)
Multiple myeloma [A] *	1/47 (2.13%)
Prostatic adenoma [A] *	2/47 (4.26%)

	Rituximab + Fludarabine + Cyclophosphamide
	Affected/At Risk (%)
Nervous system disorders	
Amnesia [A] *	1/47 (2.13%)
Cerebral ischaemia [A] *	1/47 (2.13%)
Headache [A] *	2/47 (4.26%)
Neuropathy [A] *	1/47 (2.13%)
Syncope [A] *	1/47 (2.13%)
Transient ischaemic attack [A] *	2/47 (4.26%)
Psychiatric disorders	
Anxiety [A] *	1/47 (2.13%)
Depression [A] *	1/47 (2.13%)
Insomnia [A] *	1/47 (2.13%)
Renal and urinary disorders	
Dysuria [A] *	2/47 (4.26%)
Polyuria [A] *	1/47 (2.13%)
Renal colic [A] *	1/47 (2.13%)
Renal pain [A] *	1/47 (2.13%)
Reproductive system and breast disorders	
Amenorrhoea [A] *	1/47 (2.13%)
Gynaecomasatia [A] *	1/47 (2.13%)
Respiratory, thoracic and mediastinal disorders	
Bronchospasm [A] *	1/47 (2.13%)
Chronic obstructive pulmonary disease [A] *	1/47 (2.13%)
Cough [A] *	21/47 (44.68%)

	Rituximab + Fludarabine + Cyclophosphamide
	Affected/At Risk (%)
Dyspnoea [A] *	5/47 (10.64%)
Pharyngolaryngeal pain [A] *	2/47 (4.26%)
Pneumonitis [A] *	3/47 (6.38%)
Rhinorrhoea [A] *	1/47 (2.13%)
Upper respiratory tract inflammation [A] *	1/47 (2.13%)
Skin and subcutaneous tissue disorders	
Erythema [A] *	3/47 (6.38%)
Hyperhidrosis [A] *	1/47 (2.13%)
Night sweats [A] *	2/47 (4.26%)
Periorbital oedema [A] *	1/47 (2.13%)
Pityriasis rosea [A] *	1/47 (2.13%)
Pruritus [A] *	2/47 (4.26%)
Rash [A] *	1/47 (2.13%)
Skin disorder [A] *	4/47 (8.51%)
Skin fissures [A] *	1/47 (2.13%)
Urticaria [A] *	1/47 (2.13%)
Surgical and medical procedures	
Ureterectomy [A] *	1/47 (2.13%)
Vascular disorders	
Aortic thrombosis [A] *	1/47 (2.13%)
Flushing [A] *	1/47 (2.13%)
Hypotension [A] *	1/47 (2.13%)

	Rituximab + Fludarabine + Cyclophosphamide
	Affected/At Risk (%)
Phlebitis [A] *	1/47 (2.13%)
Raynaud's phenomenon [A] *	1/47 (2.13%)

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA (10.1)

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 the Confidential Information be deleted and/or the publication be postponed in order to protect the Sponsor's intellectual property rights.

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