ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt
Release Date: 03/06/2016

ClinicalTrials.gov ID: NCT00532129

Study Identification

Unique Protocol ID:	MO20927
Brief Title:	A Study of MabThera (Rituximab) Plus Chlorambucil in Participants With Chronic Lymphocytic Leukemia.
Official Title:	An Open-Label Study to Characterize the Safety and Response Rate of MabThera (Rituximab) Plus Chlorambucil in Previously Untreated Patients With CD20-Positive B-Cell Chronic Lymphocytic Leukemia
Secondary IDs:	2007-000172-16 [EudraCT Number]

Study Status

Record Verification:	March 2016
Overall Status:	Completed
Study Start:	November 2007
Primary Completion:	April 2012 [Actual]
Study Completion:	April 2012 [Actual]

Sponsor/Collaborators

Sponsor:	Hoffmann-La Roche
Responsible Party:	Sponsor
Collaborators:	

Oversight

FDA Regulated?:	Yes
Applicable Trial?:	Section 801 Clinical Trial? No

	Delayed Posting? No
IND/IDE Protocol?:	No
Review Board:	Approval Status: Approved Approval Number: 07/H1008/119 Board Name: Central Manchester Research Ethics Committee Board Affiliation: National Research Ethics Service (NRES) Phone: +44 161 237 2153 Email: stephen.tebbutt@northwest.nhs.uk
Data Monitoring?:	Yes
Plan to Share Data?:	No
Oversight Authorities:	England: National Patient Safety Agency and Research Ethics Committees

Study Description

Brief Summary:	This single arm study will assess the safety and effect on response rate of a combination of rituximab and chlorambucil in previously untreated participants with B-cell chronic lymphocytic leukemia. Participants will receive 6 monthly cycles of combination treatment, followed by up to 6 cycles of chlorambucil alone. Rituximab will be administered on Day 1 of each cycle, at a dose of 375 milligrams per square meter (mg/m^2) intravenously (IV) in Cycle 1, and 500 mg/m^2 in subsequent cycles, and chlorambucil will be administered on Days 1-7 of each cycle at a dose of 10 mg/m^2/day per oral (PO).
Detailed Description:	

Conditions

Conditions:	Lymphocytic Leukemia, Chronic
Keywords:	

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 2
Intervention Model:	Single Group Assignment
Number of Arms:	1
Masking:	Open Label
Allocation:	N/A

Endpoint Classification: Safety/Efficacy Study

Enrollment: 100 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Rituximab plus Chlorambucil Participants will receive combination therapy of rituximab plus chlorambucil for first 6 cycles and then chlorambucil alone for a maximum of 6 additional cycles.	Drug: Rituximab 375mg/m^2 IV on Day 1 of Cycle 1; 500mg/m^2 on Day 1 of Cycles 2-6. Other Names: • MabThera • Rituxan Drug: Chlorambucil 10 mg/m^2/day PO on Days 1 to 7 of each cycle for a maximum of 12 cycles.

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age: 18 Years

Maximum Age:

Gender: Both

Accepts Healthy Volunteers?: No

Criteria: Inclusion Criteria:

- previously untreated participants with cluster of differentiation 20 (CD20) positive B-cell chronic lymphocytic leukemia;
- participants with progressive Binet stage B, or C requiring therapy according to National Cancer Institute (NCI) criteria;
- Eastern Cooperative Oncology Group (ECOG) performance status <=2.

Exclusion Criteria:

- previous treatment for Chronic Lymphocytic Leukaemia (CLL);
- known concomitant hematological malignancy;
- transformation to aggressive B-cell malignancy;
- history of severe cardiac disease;
- known hypersensitivity or anaphylactic reactions to murine antibodies.

Contacts/Locations

Study Officials: Clinical Trials
Study Director
Hoffmann-La Roche

Locations: United Kingdom
Leeds, United Kingdom, LS9 7TF

Liverpool, United Kingdom, L7 8XP

Leicester, United Kingdom, LE1 5WW

Birmingham, United Kingdom, B9 5SS

Bournemouth, United Kingdom, BH7 7DW

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Cambridge, United Kingdom, CB2 0QQ

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Sutton, United Kingdom, SM2 5PT

Wakefield, United Kingdom, WF1 4DG

Cottingham, United Kingdom, HU16 5JQ

London, United Kingdom, NW1 2PG

References

Citations:

Links:

Study Data/Documents:

Participant Flow

Reporting Groups

	Description
Rituximab + Chlorambucil	Participants received combination therapy of rituximab plus chlorambucil for first 6 cycles (28 day cycles). Participants who did not achieve complete response (CR) after Cycle 6 then received chlorambucil alone from Cycle 7 onwards until either they achieved a CR or for a maximum of 6 additional cycles. Rituximab: 375 milligrams per square meter (mg/m^2) intravenous (IV) infusion on Day 1 of Cycle 1; 500 mg/m^2 on Day 1 of Cycles 2-6. Chlorambucil: 10 milligrams per square meter per day (mg/m^2/day) oral administration (PO) on Days 1 to 7 of Cycles 1-6; 10 mg/m^2/day PO on Days 1 to 7 of Cycles 7-12, if applicable.

Treatment Period

	Rituximab + Chlorambucil
Started	100
Completed	51
Not Completed	49
Adverse event/Serious adverse event	25
Physician Decision	15
Disease progression	3
Protocol Violation	1
Unspecified	5

Follow-up Period

	Rituximab + Chlorambucil
Started	98
Completed	33
Not Completed	65
Adverse event/Serious adverse event	1
Disease progression	57
Lost to Follow-up	1
Unspecified	6

Baseline Characteristics

Analysis Population Description

Full analysis set (FAS) comprised all participants recruited into the study and known to have received at least one dose of study treatment.

Reporting Groups

	Description
Rituximab + Chlorambucil	Participants received combination therapy of rituximab plus chlorambucil for first 6 cycles. Participants who did not achieve CR after Cycle 6 then received chlorambucil alone from Cycle 7 onwards until either they achieved a CR or for a maximum of 6 additional cycles. Rituximab: 375 mg/m^2 IV infusion on Day 1 of Cycle 1; 500 mg/m^2 on Day 1 of Cycles 2-6. Chlorambucil: 10 mg/m^2/day PO on Days 1 to 7 of Cycles 1-6; 10 mg/m^2/day PO on Days 1 to 7 of Cycles 7-12, if applicable.

Baseline Measures

	Rituximab + Chlorambucil
Number of Participants	100
Age, Continuous [units: years] Mean (Standard Deviation)	69.5 (8.3)
Gender, Male/Female [units: participants]	
Female	34
Male	66

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Percentage of Participants With Treatment-Emergent Adverse Events (AEs)
Measure Description	An AE was any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. A serious AE (SAE) was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Treatment-emergent are events between first dose of study drug and up to 56 days from the beginning of the last treatment cycle that were absent before treatment or that worsened relative to pretreatment state. AEs included both SAEs as well as non-serious AEs.
Time Frame	First administration of study treatment up to 56 days after the beginning of the last treatment cycle (up to 365 days)
Safety Issue?	No

Analysis Population Description
FAS.

Reporting Groups

	Description
Rituximab + Chlorambucil	Participants received combination therapy of rituximab plus chlorambucil for first 6 cycles. Participants who did not achieve CR after Cycle 6 then received chlorambucil alone from Cycle 7 onwards until either they achieved a CR or for a maximum of 6 additional cycles. Rituximab: 375 mg/m^2 IV infusion on Day 1 of Cycle 1; 500 mg/m^2 on Day 1 of Cycles 2-6. Chlorambucil: 10 mg/m^2/day PO on Days 1 to 7 of Cycles 1-6; 10 mg/m^2/day PO on Days 1 to 7 of Cycles 7-12, if applicable.

Measured Values

	Rituximab + Chlorambucil
Number of Participants Analyzed	100
Percentage of Participants With Treatment-Emergent Adverse Events (AEs) [units: percentage of participants]	99

2. Secondary Outcome Measure:

Measure Title	Percentage of Participants With Best Overall Response (BOR) of Clinical CR or Confirmed CR
Measure Description	Clinical CR was achieved if all of the following criteria were met: a)Absence of lymphadenopathy (LD) by physical examination (PE) and Computed Tomography (CT) scan (all lymph nodes less than [<] 1.5 centimeters [cm] in diameter), b)No hepatomegaly (HM)/splenomegaly (SM) by PE/CT scan, c)Absence of B symptoms (unexplained fever greater than [>] 38 degrees [°] Centigrade [C], drenching night sweats/>10 percent [%] body weight loss in the last 6 months), d)Normal Complete Blood Count (CBC) (i. Leukocytes (Leuk) greater than or equal to [≥] 1.5×10^9 per liter (/L), ii. Platelets (Plat) >100×10^9/L, and iii. Haemoglobin (Hb) >11.0 grams per deciliter [g/dL]) and e)Once clinical, radiological and laboratory evaluations demonstrated CR, bone marrow (BM) biopsy and aspirate were performed 8 weeks later for confirmation; BM sample: normocellular for age, <30% of the cells being lymphocytes (Lym) and lymphoid nodules (LN) absent was considered as a confirmed CR.
Time Frame	Baseline until disease progression or death up to approximately 2.5 years (assessed at Baseline, Cycle 4 Day 1, Day 1 of Cycles 7-12, and thereafter every 3 months up to approximately 2.5 years; cycle length = 28 days)
Safety Issue?	No

Analysis Population Description
FAS.

Reporting Groups

	Description
Rituximab + Chlorambucil	Participants received combination therapy of rituximab plus chlorambucil for first 6 cycles. Participants who did not achieve CR after Cycle 6 then received chlorambucil alone from Cycle 7 onwards until either they achieved a CR or for a maximum of 6 additional cycles. Rituximab: 375 mg/m^2 IV infusion on Day 1 of Cycle 1; 500 mg/m^2 on Day 1 of Cycles 2-6. Chlorambucil: 10 mg/m^2/day PO on Days 1 to 7 of Cycles 1-6; 10 mg/m^2/day PO on Days 1 to 7 of Cycles 7-12, if applicable.

Measured Values

	Rituximab + Chlorambucil
Number of Participants Analyzed	100
Percentage of Participants With Best Overall Response (BOR) of Clinical CR or Confirmed CR [units: percentage of participants]	
Clinical CR	37.0
Confirmed CR	10.0
Clinical CR or Confirmed CR	47.0

3. Secondary Outcome Measure:

Measure Title	Percentage of Participants With BOR of Partial Response (PR)
Measure Description	PR was achieved if all of the following criteria were met: a)≥50% decrease in Lym count from the baseline value, b)≥50% reduction in LD by CT scan, c)≥50% reduction in size of liver/spleen by PE/CT scan and at least 1 of the following for a minimum of 8 weeks: i. Leuk ≥1.5×10^9/L or 50% improvement over baseline, ii. Plat >100×10^9/L or 50% improvement over baseline and iii. Hb >11.0 g/dL or 50% improvement over baseline without transfusion. Participants who fulfilled criteria for CR with persistent anemia/thrombocytopenia were considered in PRs. CR was achieved if all of the criteria were fulfilled for ≥8 weeks: a)Absence of LD by PE and CT scan, b)No HM/SM by PE/CT, c)Absence of B symptoms, d)Normal CBC, and e)BM biopsy: normocellular for age, <30% of the cells being Lym and LN absent.
Time Frame	Baseline until disease progression or death up to approximately 2.5 years (assessed at Baseline, Cycle 4 Day 1, Day 1 of Cycles 7-12, and thereafter every 3 months up to approximately 2.5 years; cycle length = 28 days)
Safety Issue?	No

Analysis Population Description

FAS.

Reporting Groups

	Description
Rituximab + Chlorambucil	Participants received combination therapy of rituximab plus chlorambucil for first 6 cycles. Participants who did not achieve CR after Cycle 6 then received chlorambucil alone from Cycle 7 onwards until either they achieved a CR or for a maximum of 6 additional cycles. Rituximab: 375 mg/m^2 IV infusion on Day 1 of Cycle 1; 500 mg/m^2 on Day 1 of Cycles 2-6. Chlorambucil: 10 mg/m^2/day PO on Days 1 to 7 of Cycles 1-6; 10 mg/m^2/day PO on Days 1 to 7 of Cycles 7-12, if applicable.

Measured Values

	Rituximab + Chlorambucil
Number of Participants Analyzed	100
Percentage of Participants With BOR of Partial Response (PR) [units: percentage of participants]	68.0

4. Secondary Outcome Measure:

Measure Title	Percentage of Participants With BOR of Nodular Partial Response (nPR)
Measure Description	CR was achieved if all of the following criteria were met for ≥8 weeks: a)Absence of LD by PE and CT scan, b)No HM/SM by PE/CT scan, c)Absence of B symptoms, d)Normal CBC, and e)BM biopsy: normocellular for age, <30% of the cells being Lym and LN absent. Participants with nPR were those who satisfied all of the CR criteria except for the BM, where LN could be identified histologically.
Time Frame	Baseline until disease progression or death up to approximately 2.5 years (assessed at Baseline, Cycle 4 Day 1, Day 1 of Cycles 7-12, and thereafter every 3 months up to approximately 2.5 years; cycle length = 28 days)
Safety Issue?	No

Analysis Population Description
FAS.

Reporting Groups

	Description
Rituximab + Chlorambucil	Participants received combination therapy of rituximab plus chlorambucil for first 6 cycles. Participants who did not achieve CR after Cycle 6 then received chlorambucil alone from Cycle 7 onwards until either they achieved a CR or for a maximum of 6 additional cycles. Rituximab: 375 mg/m^2 IV infusion on Day 1 of Cycle 1; 500 mg/m^2 on Day 1 of Cycles 2-6. Chlorambucil: 10 mg/m^2/day PO on Days 1 to 7 of Cycles 1-6; 10 mg/m^2/day PO on Days 1 to 7 of Cycles 7-12, if applicable.

Measured Values

	Rituximab + Chlorambucil
Number of Participants Analyzed	100
Percentage of Participants With BOR of Nodular Partial Response (nPR) [units: percentage of participants]	6.0

5. Secondary Outcome Measure:

Measure Title	Percentage of Participants With BOR of Progressive Disease (PD)
Measure Description	PD is considered if 1 of the following criteria is met: a)≥50% increase in sum of the products of ≥2 lymph nodes compared to their smallest size (at least one ≥2 cm in diameter) or appearance of new lymph nodes/extranodal lesions, b)≥50% increase in the size of hepatosplenomegaly (HSM) as determined by PE/CT scan; appearance of palpable HM/SM that was not previously present, c)≥50% increase in the absolute number of circulating Lym to ≥5×10^9/L, d)Transformation to a more aggressive histology. Symptomatic deterioration (evident in clinical symptoms but not supported by tumor assessments), in such cases, the determination of clinical progression was based on symptomatic deterioration.
Time Frame	Baseline until disease progression or death up to approximately 2.5 years (assessed at Baseline, Cycle 4 Day 1, Day 1 of Cycles 7-12, and thereafter every 3 months up to approximately 2.5 years; cycle length = 28 days)
Safety Issue?	No

Analysis Population Description
FAS.

Reporting Groups

	Description
Rituximab + Chlorambucil	Participants received combination therapy of rituximab plus chlorambucil for first 6 cycles. Participants who did not achieve CR after Cycle 6 then received chlorambucil alone from Cycle 7 onwards until either they achieved a CR or for a maximum of 6 additional cycles. Rituximab: 375 mg/m^2 IV infusion on Day 1 of Cycle 1; 500 mg/m^2 on Day 1 of Cycles 2-6. Chlorambucil: 10 mg/m^2/day PO on Days 1 to 7 of Cycles 1-6; 10 mg/m^2/day PO on Days 1 to 7 of Cycles 7-12, if applicable.

Measured Values

	Rituximab + Chlorambucil
Number of Participants Analyzed	100
Percentage of Participants With BOR of Progressive Disease (PD)	4.0

	Rituximab + Chlorambucil
[units: percentage of participants]	

6. Secondary Outcome Measure:

Measure Title	Percentage of Participants With BOR of Stable Disease (SD)
Measure Description	Participants without CR/PR or PD were considered having a tumor response of SD. CR: a) Absence of LD by PE and CT, b) No HM/SM by PE/CT, c) Absence of B symptoms, d) Normal CBC, and e) BM biopsy: normocellular for age, <30% of the cells being Lym and LN absent. PR: a) ≥50% decrease in Lym count from baseline, b) ≥50% reduction in LD, c) ≥50% reduction in size of liver/spleen by PE/CT and ≥1 of the following for at least 8 weeks: i. Leuk ≥1.5×10^9/L or 50% improvement over baseline, ii. Plat >100×10^9/L or 50% improvement over baseline and iii. Hb >11.0 g/dL or 50% improvement over baseline without transfusion. PD: a) ≥50% increase in sum of the products of ≥2 lymph nodes compared to their smallest size or appearance of new lymph nodes/extranodal lesions, or b) ≥50% increase in the size of HSM; new appearance of palpable HM/SM, or c) ≥50% increase in the absolute number of circulating Lym to ≥5×10^9/L, or d) Transformation to a more aggressive histology.
Time Frame	Baseline until disease progression or death up to approximately 2.5 years (assessed at Baseline, Cycle 4 Day 1, Day 1 of Cycles 7-12, and thereafter every 3 months up to approximately 2.5 years; cycle length = 28 days)
Safety Issue?	No

Analysis Population Description
FAS.

Reporting Groups

	Description
Rituximab + Chlorambucil	Participants received combination therapy of rituximab plus chlorambucil for first 6 cycles. Participants who did not achieve CR after Cycle 6 then received chlorambucil alone from Cycle 7 onwards until either they achieved a CR or for a maximum of 6 additional cycles. Rituximab: 375 mg/m^2 IV infusion on Day 1 of Cycle 1; 500 mg/m^2 on Day 1 of Cycles 2-6. Chlorambucil: 10 mg/m^2/day PO on Days 1 to 7 of Cycles 1-6; 10 mg/m^2/day PO on Days 1 to 7 of Cycles 7-12, if applicable.

Measured Values

	Rituximab + Chlorambucil
Number of Participants Analyzed	100
Percentage of Participants With BOR of Stable Disease (SD) [units: percentage of participants]	11.0

7. Secondary Outcome Measure:

Measure Title	Percentage of Participants With Objective Response (CR or PR)
Measure Description	Objective response was defined as a tumor response of CR or PR. CR was achieved if all of the criteria were met for ≥8 weeks: a)Absence of LD by PE and CT scan, b)No HM/SM by PE/CT scan, c)Absence of B symptoms, d)Normal CBC, and e)BM biopsy: normocellular for age, <30% of the cells being Lym and LN absent. PR was achieved if all of the criteria were met: a)≥50% decrease in Lymp count from the baseline value, b)≥50% reduction in LD by CT scan, c)≥50% reduction in size of liver/spleen by PE/CT scan and at least 1 of the following for a minimum of 8 weeks: i. Leuk ≥1.5×10^9/L or 50% improvement over baseline, ii. Plat >100×10^9/L or 50% improvement over baseline and iii. Hb >11.0 g/dL or 50% improvement over baseline without transfusion. Participants who fulfilled criteria for CR with persistent anemia/thrombocytopenia were considered PRs.
Time Frame	Baseline until disease progression or death up to approximately 2.5 years (assessed at Baseline, Cycle 4 Day 1, Day 1 of Cycles 7-12, and thereafter every 3 months up to approximately 2.5 years; cycle length = 28 days)
Safety Issue?	No

Analysis Population Description

FAS.

Reporting Groups

	Description
Rituximab + Chlorambucil	Participants received combination therapy of rituximab plus chlorambucil for first 6 cycles. Participants who did not achieve CR after Cycle 6 then received chlorambucil alone from Cycle 7 onwards until either they achieved a CR or for a maximum of 6 additional cycles. Rituximab: 375 mg/m^2 IV infusion on Day 1 of Cycle 1; 500 mg/m^2 on Day 1 of Cycles 2-6. Chlorambucil: 10 mg/m^2/day PO on Days 1 to 7 of Cycles 1-6; 10 mg/m^2/day PO on Days 1 to 7 of Cycles 7-12, if applicable.

Measured Values

	Rituximab + Chlorambucil
Number of Participants Analyzed	100
Percentage of Participants With Objective Response (CR or PR) [units: percentage of participants] Number (95% Confidence Interval)	84.0 (75.3 to 90.6)

8. Secondary Outcome Measure:

Measure Title	Percentage of Participant With Disease Progression or Death
Measure Description	PD is considered if 1 of the following criteria is met: a)≥50% increase in sum of the products of ≥2 lymph nodes compared to their smallest size (at least one ≥2 cm in diameter) or appearance of new lymph nodes/extranodal lesions, b)≥50% increase in the size of HSM as determined by PE/CT scan; appearance of palpable HM/SM that was not previously present, c)≥50% increase in the absolute number of circulating Lym to ≥5×10^9/L, d)Transformation to a more aggressive histology. Symptomatic deterioration (evident in clinical symptoms but not supported by tumor assessments), in such cases, the determination of clinical progression was based on symptomatic deterioration.
Time Frame	Baseline until disease progression or death up to approximately 2.5 years (assessed at Baseline, Cycle 4 Day 1, Day 1 of Cycles 7-12, and thereafter every 3 months up to approximately 2.5 years; cycle length = 28 days)
Safety Issue?	No

Analysis Population Description
FAS.

Reporting Groups

	Description
Rituximab + Chlorambucil	Participants received combination therapy of rituximab plus chlorambucil for first 6 cycles. Participants who did not achieve CR after Cycle 6 then received chlorambucil alone from Cycle 7 onwards until either they achieved a CR or for a maximum of 6 additional cycles. Rituximab: 375 mg/m^2 IV infusion on Day 1 of Cycle 1; 500 mg/m^2 on Day 1 of Cycles 2-6. Chlorambucil: 10 mg/m^2/day PO on Days 1 to 7 of Cycles 1-6; 10 mg/m^2/day PO on Days 1 to 7 of Cycles 7-12, if applicable.

Measured Values

	Rituximab + Chlorambucil
Number of Participants Analyzed	100
Percentage of Participant With Disease Progression or Death [units: percentage of participants]	68.0

9. Secondary Outcome Measure:

Measure Title	Progression Free Survival (PFS) Time

Measure Description	PFS was defined as the interval (in days) from trial treatment start date to earlier of the date of first tumor response assessment of PD or date of death by any cause. Participants who experienced none of these events or who were lost to follow-up at the time of analysis were censored on last date when they were assessed for tumor response. PD is considered if 1 of the following criteria is met: a)≥50% increase in sum of products of ≥2 lymph nodes compared to their smallest size (at least one ≥2 cm in diameter) or appearance of new lymph nodes/extranodal lesions, b)≥50% increase in the size of HSM as determined by PE/CT; appearance of palpable HM/SM that was not previously present, c)≥50% increase in the number of circulating Lym to ≥5×10^9/L, d)Transformation to a more aggressive histology. Symptomatic deterioration (evident in clinical symptoms but not supported by tumor assessments), in such cases, the determination of clinical progression was based on symptomatic deterioration.
Time Frame	Baseline until disease progression or death up to approximately 2.5 years (assessed at Baseline, Cycle 4 Day 1, Day 1 of Cycles 7-12, and thereafter every 3 months up to approximately 2.5 years; cycle length = 28 days)
Safety Issue?	No

Analysis Population Description
FAS.

Reporting Groups

	Description
Rituximab + Chlorambucil	Participants received combination therapy of rituximab plus chlorambucil for first 6 cycles. Participants who did not achieve CR after Cycle 6 then received chlorambucil alone from Cycle 7 onwards until either they achieved a CR or for a maximum of 6 additional cycles. Rituximab: 375 mg/m^2 IV infusion on Day 1 of Cycle 1; 500 mg/m^2 on Day 1 of Cycles 2-6. Chlorambucil: 10 mg/m^2/day PO on Days 1 to 7 of Cycles 1-6; 10 mg/m^2/day PO on Days 1 to 7 of Cycles 7-12, if applicable.

Measured Values

	Rituximab + Chlorambucil
Number of Participants Analyzed	100
Progression Free Survival (PFS) Time [units: days] Median (95% Confidence Interval)	716.5 (500.0 to 784.0)

10. Secondary Outcome Measure:

Measure Title	Disease Free Survival (DFS) Time

Measure Description	DFS time was defined as interval (in days) from first tumor response of CR to date of first tumor response of PD, or date of death by any cause. Participants who experienced none of these events or who were lost to follow-up at the time of analysis were censored on last date when they were assessed for tumor response. CR: a) Absence of LD by PE and CT, b) No HM/SM by PE/CT, c) Absence of B symptoms, d) Normal CBC, and e) BM biopsy: normocellular for age, <30% of the cells being Lym and LN absent. PD: a) ≥50% increase in sum of the products of ≥2 lymph nodes compared to their smallest size or appearance of new lymph nodes/extranodal lesions, or b) ≥50% increase in the size of HSM; new appearance of palpable HM/SM, or c) ≥50% increase in the absolute number of circulating Lym to ≥5×10^9/L, or d) Transformation to a more aggressive histology.
Time Frame	Baseline until disease progression or death up to approximately 2.5 years (assessed at Baseline, Cycle 4 Day 1, Day 1 of Cycles 7-12, and thereafter every 3 months up to approximately 2.5 years; cycle length = 28 days)
Safety Issue?	No

Analysis Population Description

FAS population participants who achieved confirmed CR.

Reporting Groups

	Description
Rituximab + Chlorambucil	Participants received combination therapy of rituximab plus chlorambucil for first 6 cycles. Participants who did not achieve CR after Cycle 6 then received chlorambucil alone from Cycle 7 onwards until either they achieved a CR or for a maximum of 6 additional cycles. Rituximab: 375 mg/m^2 IV infusion on Day 1 of Cycle 1; 500 mg/m^2 on Day 1 of Cycles 2-6. Chlorambucil: 10 mg/m^2/day PO on Days 1 to 7 of Cycles 1-6; 10 mg/m^2/day PO on Days 1 to 7 of Cycles 7-12, if applicable.

Measured Values

	Rituximab + Chlorambucil
Number of Participants Analyzed	10
Disease Free Survival (DFS) Time [units: days] Median (95% Confidence Interval)	855.0 (290.0 to 855.0)

11. Secondary Outcome Measure:

Measure Title	Duration of Response (DoR)

Measure Description	DoR: defined as interval (in days) from first tumor response (of CR/PR/nPR) to earlier of date of PD/death. Participants without PD/death or who were lost to follow-up were censored. CR: a)Absence of LD by PE and CT, b)No HM/SM by PE/CT, c)Absence of B symptoms, d)Normal CBC, and e)BM biopsy: normocellular for age, <30% of the cells being Lym and LN absent. PR: a)≥50% decrease in Lym count from baseline value, b)≥50% reduction in LD, c)≥50% reduction in size of liver/spleen by PE/CT scan and d)Leuk, Plat and Hb ≥1.5×10^9/L, >100×10^9/L and >11.0 g/dL, respectively or 50% improvement (of all the 3) over baseline value. nPR: participants who satisfied all of CR criteria except for BM, where LN could be identified. PD: a)≥50% increase in sum of the products of ≥2 lymph nodes or appearance of new lymph nodes/extranodal lesions, or b)≥50% increase in size of HSM; new appearance of palpable HM/SM, or c)≥50% increase in number of Lym, or d)Transformation to a more aggressive histology.
Time Frame	Baseline until disease progression or death up to approximately 2.5 years (assessed at Baseline, Cycle 4 Day 1, Day 1 of Cycles 7-12, and thereafter every 3 months up to approximately 2.5 years; cycle length = 28 days)
Safety Issue?	No

Analysis Population Description

FAS population participants who achieved confirmed CR, PR or nPR.

Reporting Groups

	Description
Rituximab + Chlorambucil	Participants received combination therapy of rituximab plus chlorambucil for first 6 cycles. Participants who did not achieve CR after Cycle 6 then received chlorambucil alone from Cycle 7 onwards until either they achieved a CR or for a maximum of 6 additional cycles. Rituximab: 375 mg/m^2 IV infusion on Day 1 of Cycle 1; 500 mg/m^2 on Day 1 of Cycles 2-6. Chlorambucil: 10 mg/m^2/day PO on Days 1 to 7 of Cycles 1-6; 10 mg/m^2/day PO on Days 1 to 7 of Cycles 7-12, if applicable.

Measured Values

	Rituximab + Chlorambucil
Number of Participants Analyzed	84
Duration of Response (DoR) [units: days] Median (95% Confidence Interval)	645.0 (561.0 to 758.0)

12. Secondary Outcome Measure:

Measure Title	Percentage of Participants Who Died
Measure Description	
Time Frame	Baseline until disease progression or death up to approximately 2.5 years (assessed at Baseline, Cycle 4 Day 1, Day 1 of Cycles 7-12, and thereafter every 3 months up to approximately 2.5 years; cycle length = 28 days)

Safety Issue?	No

Analysis Population Description
FAS.

Reporting Groups

	Description
Rituximab + Chlorambucil	Participants received combination therapy of rituximab plus chlorambucil for first 6 cycles. Participants who did not achieve CR after Cycle 6 then received chlorambucil alone from Cycle 7 onwards until either they achieved a CR or for a maximum of 6 additional cycles. Rituximab: 375 mg/m^2 IV infusion on Day 1 of Cycle 1; 500 mg/m^2 on Day 1 of Cycles 2-6. Chlorambucil: 10 mg/m^2/day PO on Days 1 to 7 of Cycles 1-6; 10 mg/m^2/day PO on Days 1 to 7 of Cycles 7-12, if applicable.

Measured Values

	Rituximab + Chlorambucil
Number of Participants Analyzed	100
Percentage of Participants Who Died [units: percentage of participants]	15.0

13. Secondary Outcome Measure:

Measure Title	Overall Survival (OS) Time
Measure Description	This was defined as the interval (number of days) from the trial treatment start date to the date of death by any cause. Participants who were alive at the time of the analysis were censored at the date of the last follow-up assessment.
Time Frame	Baseline until disease progression or death up to approximately 2.5 years (assessed at Baseline, Cycle 4 Day 1, Day 1 of Cycles 7-12, and thereafter every 3 months up to approximately 2.5 years; cycle length = 28 days)
Safety Issue?	No

Analysis Population Description
FAS.

Reporting Groups

	Description
Rituximab + Chlorambucil	Participants received combination therapy of rituximab plus chlorambucil for first 6 cycles. Participants who did not achieve CR after Cycle 6 then received chlorambucil alone from Cycle 7 onwards until either they achieved a CR or for a maximum of 6 additional cycles. Rituximab: 375 mg/m^2 IV infusion on Day 1 of Cycle 1; 500 mg/m^2 on Day 1 of Cycles 2-6. Chlorambucil: 10 mg/m^2/day PO on Days 1 to 7 of Cycles 1-6; 10 mg/m^2/day PO on Days 1 to 7 of Cycles 7-12, if applicable.

Measured Values

	Rituximab + Chlorambucil
Number of Participants Analyzed	100
Overall Survival (OS) Time [units: percentage of participants] Median (95% Confidence Interval)	NA (NA to NA) [1]

[1] Median and 95% confidence interval of OS time not available due to insufficient follow-up to allow estimation.

14. Secondary Outcome Measure:

Measure Title	Percentage of Participants Who Achieved Minimal Residual Disease (MRD) Negativity
Measure Description	MRD negativity was defined by the absence of tumor cells in bone marrow, using 4-color flow cytometry. MRD was assessed in participants with a confirmed CR. CR was achieved if all of the following criteria were met for ≥8 weeks: a)Absence of LD by PE and CT scan, b)No HM/SM by PE/CT scan, c)Absence of B symptoms, d)Normal CBC, and e)BM biopsy: normocellular for age, <30% of the cells being Lym and LN absent.
Time Frame	Baseline until disease progression or death up to approximately 2.5 years (assessed at Baseline, Cycle 4 Day 1, Day 1 of Cycles 7-12, and thereafter every 3 months up to approximately 2.5 years; cycle length = 28 days)
Safety Issue?	No

Analysis Population Description

FAS population participants who achieved confirmed CR.

Reporting Groups

	Description
Rituximab + Chlorambucil	Participants received combination therapy of rituximab plus chlorambucil for first 6 cycles. Participants who did not achieve CR after Cycle 6 then received chlorambucil alone from Cycle 7 onwards until either they achieved a CR or for a maximum of 6 additional cycles. Rituximab: 375 mg/m^2 IV infusion on Day 1 of Cycle 1; 500 mg/m^2 on Day 1 of Cycles 2-6. Chlorambucil: 10 mg/m^2/day PO on Days 1 to 7 of Cycles 1-6; 10 mg/m^2/day PO on Days 1 to 7 of Cycles 7-12, if applicable.

Measured Values

	Rituximab + Chlorambucil
Number of Participants Analyzed	10
Percentage of Participants Who Achieved Minimal Residual Disease (MRD) Negativity [units: percentage of participants]	0.0

15. Secondary Outcome Measure:

Measure Title	Mean Change From Baseline (CFB) in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) Scores
Measure Description	EORTC QLQ-C30: included global health status (GHS)/quality of life (QOL), functional scales (physical, role, cognitive, emotional, and social), symptom scales (fatigue, pain, nausea/vomiting), and single items (dyspnea, appetite loss, insomnia, constipation, diarrhea, and financial difficulties). Most questions used a 4- point scale (1 'Not at All' to 4 'Very Much'); 2 questions used a 7-point scale (1 'Very Poor' to 7 'Excellent'). Scores were averaged and transformed to 0-100 scale; a higher score for Global QoI/functional scales=better level of QoL/functioning, or a higher score for symptom scale=greater degree of symptoms.
Time Frame	Baseline, Day 1 of Cycles 5 and 11, end of follow-up (FU) (24 month [m] FU visit, up to approximately 3 years)
Safety Issue?	No

Analysis Population Description

FAS. Number of participants analyzed = number of participants evaluable for this outcome and n=number of participants evaluable at the specified time point.

Reporting Groups

	Description
Rituximab + Chlorambucil	Participants received combination therapy of rituximab plus chlorambucil for first 6 cycles. Participants who did not achieve CR after Cycle 6 then received chlorambucil alone from Cycle 7 onwards until either they achieved a CR or for a maximum of 6 additional cycles. Rituximab: 375 mg/m^2 IV infusion on Day 1 of Cycle 1; 500 mg/m^2 on Day 1 of Cycles 2-6. Chlorambucil: 10 mg/m^2/day PO on Days 1 to 7 of Cycles 1-6; 10 mg/m^2/day PO on Days 1 to 7 of Cycles 7-12, if applicable.

Measured Values

	Rituximab + Chlorambucil
Number of Participants Analyzed	91

	Rituximab + Chlorambucil
Mean Change From Baseline (CFB) in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) Scores [units: units on scale] Mean (Standard Deviation)	
GHS/QoL score-baseline (n=91)	65.7 (21.8)
CFB in GHS/QoL Score-Cycle 5 (n=59)	6.4 (21.7)
CFB in GHS/QoL Score-Cycle 11 (n=40)	6.2 (16.9)
CFB in GHS/QoL Score-24m FU (n=17)	2.0 (15.2)
Physical functioning score-baseline (n=91)	77.0 (22.3)
CFB in physical functioning score-Cycle 5 (n=59)	1.0 (15.3)
CFB in physical functioning score-Cycle 11 (n=40)	3.4 (22.0)
CFB in physical functioning score-24m FU (n=17)	-2.0 (10.2)
Role functioning score-baseline (n=91)	73.4 (31.6)
CFB in role functioning score-Cycle 5 (n=59)	0.0 (28.9)
CFB in role functioning score-Cycle 11 (n=40)	3.8 (32.1)
CFB in role functioning score-24m FU (n=17)	3.9 (20.0)
Emotional functioning score-baseline (n=91)	82.5 (18.1)
CFB in emotional functioning score-Cycle 5 (n=59)	1.0 (16.5)
CFB in emotional functioning score-Cycle 11 (n=40)	-0.1 (18.1)
CFB in emotional functioning score-24m FU (n=17)	0.5 (17.3)
Cognitive functioning score-baseline (n=91)	84.1 (19.1)
CFB in cognitive functioning score-Cycle 5 (n=59)	-1.9 (15.4)
CFB in cognitive functioning-Cycle 11 (n=40)	-0.4 (18.8)
CFB in cognitive functioning-24m FU (n=17)	5.2 (18.0)
Social functioning score-baseline (n=91)	82.2 (24.2)
CFB in social functioning score-Cycle 5 (n=59)	2.5 (22.5)
CFB in social functioning score-Cycle 11 (n=40)	0.0 (27.9)

	Rituximab + Chlorambucil
CFB in social functioning score-at 24m FU (n=17)	5.2 (19.9)
Fatigue score-baseline (n=91)	33.4 (25.7)
CFB in fatigue score-Cycle 5 (n=59)	-1.4 (24.9)
CFB in fatigue score-Cycle 11 (n=40)	-6.1 (27.7)
CFB in fatigue score-24m FU (n=17)	-5.6 (22.2)
Nausea/vomiting score-baseline (n=91)	6.2 (16.2)
CFB in nausea/vomiting score-Cycle 5 (n=59)	1.7 (20.9)
CFB in nausea/vomiting score-Cycle 11 (n=40)	0.4 (20.8)
CFB in nausea/vomiting score-24m FU (n=17)	-2.9 (8.8)
Pain score-baseline (n=91)	17.8 (27.0)
CFB in pain score-Cycle 5 (n=59)	-3.4 (28.8)
CFB in pain score-Cycle 11 (n=40)	-1.3 (33.2)
CFB in pain score-24m FU (n=17)	0.0 (31.2)

Statistical Analysis 1 for Mean Change From Baseline (CFB) in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) Scores

Statistical Analysis Overview	Comparison Groups	Rituximab + Chlorambucil
	Comments	CFB in GHS/QoL statistical analysis at Cycle 5.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	=0.029
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Statistical Analysis 2 for Mean Change From Baseline (CFB) in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) Scores

Statistical Analysis Overview	Comparison Groups	Rituximab + Chlorambucil
	Comments	CFB in GHS/QoL statistical analysis at Cycle 11.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	=0.027
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Statistical Analysis 3 for Mean Change From Baseline (CFB) in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) Scores

Statistical Analysis Overview	Comparison Groups	Rituximab + Chlorambucil
	Comments	CFB in GHS/QoL statistical analysis at end of FU.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	=0.602
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Statistical Analysis 4 for Mean Change From Baseline (CFB) in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) Scores

Statistical Analysis Overview	Comparison Groups	Rituximab + Chlorambucil
	Comments	CFB in physical functioning statistical analysis at Cycle 5.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	=0.631
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Statistical Analysis 5 for Mean Change From Baseline (CFB) in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) Scores

Statistical Analysis Overview	Comparison Groups	Rituximab + Chlorambucil
	Comments	CFB in physical functioning statistical analysis at Cycle 11.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	=0.339
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Statistical Analysis 6 for Mean Change From Baseline (CFB) in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) Scores

Statistical Analysis Overview	Comparison Groups	Rituximab + Chlorambucil
	Comments	CFB in physical functioning statistical analysis at end of FU.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	=0.440
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Statistical Analysis 7 for Mean Change From Baseline (CFB) in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) Scores

Statistical Analysis Overview	Comparison Groups	Rituximab + Chlorambucil
	Comments	CFB in role functioning statistical analysis at Cycle 5.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	=1.000
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Statistical Analysis 8 for Mean Change From Baseline (CFB) in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) Scores

Statistical Analysis Overview	Comparison Groups	Rituximab + Chlorambucil
	Comments	CFB in role functioning statistical analysis at Cycle 11.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	=0.465
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Statistical Analysis 9 for Mean Change From Baseline (CFB) in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) Scores

Statistical Analysis Overview	Comparison Groups	Rituximab + Chlorambucil
	Comments	CFB in role functioning statistical analysis at end of FU.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	=0.431
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Statistical Analysis 10 for Mean Change From Baseline (CFB) in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) Scores

Statistical Analysis Overview	Comparison Groups	Rituximab + Chlorambucil
	Comments	CFB in emotional functioning statistical analysis at Cycle 5.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	=0.650
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Statistical Analysis 11 for Mean Change From Baseline (CFB) in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) Scores

Statistical Analysis Overview	Comparison Groups	Rituximab + Chlorambucil
	Comments	CFB in emotional functioning statistical analysis at Cycle 11.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	=0.980
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Statistical Analysis 12 for Mean Change From Baseline (CFB) in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) Scores

Statistical Analysis Overview	Comparison Groups	Rituximab + Chlorambucil
	Comments	CFB in emotional functioning statistical analysis at end of FU.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	=0.906
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Statistical Analysis 13 for Mean Change From Baseline (CFB) in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) Scores

Statistical Analysis Overview	Comparison Groups	Rituximab + Chlorambucil
	Comments	CFB in cognitive functioning statistical analysis at Cycle 5.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	=0.381
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Statistical Analysis 14 for Mean Change From Baseline (CFB) in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) Scores

Statistical Analysis Overview	Comparison Groups	Rituximab + Chlorambucil
	Comments	CFB in cognitive functioning statistical analysis at Cycle 11.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	=0.886
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Statistical Analysis 15 for Mean Change From Baseline (CFB) in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) Scores

Statistical Analysis Overview	Comparison Groups	Rituximab + Chlorambucil
	Comments	CFB in cognitive functioning statistical analysis at end of FU.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	=0.264
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Statistical Analysis 16 for Mean Change From Baseline (CFB) in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) Scores

Statistical Analysis Overview	Comparison Groups	Rituximab + Chlorambucil
	Comments	CFB in social functioning statistical analysis at Cycle 5.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	=0.424
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Statistical Analysis 17 for Mean Change From Baseline (CFB) in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) Scores

Statistical Analysis Overview	Comparison Groups	Rituximab + Chlorambucil
	Comments	CFB in social functioning statistical analysis at Cycle 11.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	=1.000
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Statistical Analysis 18 for Mean Change From Baseline (CFB) in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) Scores

Statistical Analysis Overview	Comparison Groups	Rituximab + Chlorambucil
	Comments	CFB in social functioning statistical analysis at end of FU.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	=0.312
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Statistical Analysis 19 for Mean Change From Baseline (CFB) in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) Scores

Statistical Analysis Overview	Comparison Groups	Rituximab + Chlorambucil
	Comments	CFB in fatigue statistical analysis at Cycle 5.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	=0.664
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Statistical Analysis 20 for Mean Change From Baseline (CFB) in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) Scores

Statistical Analysis Overview	Comparison Groups	Rituximab + Chlorambucil
	Comments	CFB in fatigue functioning statistical analysis at Cycle 11.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	=0.170
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Statistical Analysis 21 for Mean Change From Baseline (CFB) in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) Scores

Statistical Analysis Overview	Comparison Groups	Rituximab + Chlorambucil
	Comments	CFB in fatigue statistical analysis at end of FU.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	=0.318
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Statistical Analysis 22 for Mean Change From Baseline (CFB) in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) Scores

Statistical Analysis Overview	Comparison Groups	Rituximab + Chlorambucil
	Comments	CFB in Nausea/vomiting statistical analysis at Cycle 5.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	=0.536
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Statistical Analysis 23 for Mean Change From Baseline (CFB) in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) Scores

Statistical Analysis Overview	Comparison Groups	Rituximab + Chlorambucil
	Comments	CFB in nausea/vomiting statistical analysis at Cycle 11.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	=0.900
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Statistical Analysis 24 for Mean Change From Baseline (CFB) in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) Scores

Statistical Analysis Overview	Comparison Groups	Rituximab + Chlorambucil
	Comments	CFB in nausea/vomiting statistical analysis at end of FU.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	=0.188
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Statistical Analysis 25 for Mean Change From Baseline (CFB) in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) Scores

Statistical Analysis Overview	Comparison Groups	Rituximab + Chlorambucil
	Comments	CFB in pain statistical analysis at Cycle 5.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	=0.370
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Statistical Analysis 26 for Mean Change From Baseline (CFB) in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) Scores

Statistical Analysis Overview	Comparison Groups	Rituximab + Chlorambucil
	Comments	CFB in pain statistical analysis at Cycle 11.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	=0.813
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Statistical Analysis 27 for Mean Change From Baseline (CFB) in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) Scores

Statistical Analysis Overview	Comparison Groups	Rituximab + Chlorambucil
	Comments	CFB in pain statistical analysis at end of FU.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	=1.000
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Reported Adverse Events

Time Frame	First administration of study treatment up to 56 days after the beginning of the last treatment cycle (up to 365 days)
Additional Description	[Not specified]

Reporting Groups

	Description
Rituximab + Chlorambucil	Participants received combination therapy of rituximab plus chlorambucil for first 6 cycles. Participants who did not achieve CR after Cycle 6 then received chlorambucil alone from Cycle 7 onwards until either they achieved a CR or for a maximum of 6 additional cycles. Rituximab: 375 mg/m^2 IV infusion on Day 1 of Cycle 1; 500 mg/m^2 on Day 1 of Cycles 2-6. Chlorambucil: 10 mg/m^2/day PO on Days 1 to 7 of Cycles 1-6; 10 mg/m^2/day PO on Days 1 to 7 of Cycles 7-12, if applicable.

Serious Adverse Events

	Rituximab + Chlorambucil
	Affected/At Risk (%)
Total	39/100 (39%)
Blood and lymphatic system disorders	
Anaemia [A] *	1/100 (1%)

	Rituximab + Chlorambucil
	Affected/At Risk (%)
Febrile neutropenia [A] *	5/100 (5%)
Haemolytic anaemia [A] *	1/100 (1%)
Gastrointestinal disorders	
Diarrhoea [A] *	1/100 (1%)
Nausea [A] *	1/100 (1%)
Neutropenic colitis [A] *	1/100 (1%)
Vomiting [A] *	2/100 (2%)
General disorders	
Infusion related reaction [A] *	3/100 (3%)
Oedema peripheral [A] *	1/100 (1%)
Pyrexia [A] *	2/100 (2%)
Hepatobiliary disorders	
Cholecystitis acute [A] *	1/100 (1%)
Immune system disorders	
Anaphylactic reaction [A] *	1/100 (1%)
Cytokine release syndrome [A] *	2/100 (2%)
Infections and infestations	
Anal infection [A] *	1/100 (1%)
Bacterial sepsis [A] *	1/100 (1%)
Cellulitis [A] *	1/100 (1%)
Encephalitis viral [A] *	1/100 (1%)
Lower respiratory tract infection [A] *	1/100 (1%)
Lung infection [A] *	1/100 (1%)

	Rituximab + Chlorambucil
	Affected/At Risk (%)
Neutropenic sepsis [A] *	4/100 (4%)
Oral candidiasis [A] *	1/100 (1%)
Pneumonia [A] *	2/100 (2%)
Pseudomonal bacteraemia [A] *	1/100 (1%)
Staphylococcal skin infection [A] *	1/100 (1%)
Upper respiratory tract infection [A] *	1/100 (1%)
Investigations	
Staphylococcal indentification test positive [A] *	1/100 (1%)
Metabolism and nutrition disorders	
Dehydration [A] *	1/100 (1%)
Hypokalaemia [A] *	1/100 (1%)
Malnutrition [A] *	1/100 (1%)
Musculoskeletal and connective tissue disorders	
Back pain [A] *	2/100 (2%)
Joint swelling [A] *	2/100 (2%)
Nervous system disorders	
Autonomic nervous system imbalance [A] *	1/100 (1%)
Cerebral infarction [A] *	1/100 (1%)
Dizziness [A] *	1/100 (1%)
Loss of consciousness [A] *	1/100 (1%)
Myoclonus [A] *	1/100 (1%)
Syncope [A] *	1/100 (1%)

	Rituximab + Chlorambucil
	Affected/At Risk (%)
Reproductive system and breast disorders	
Scrotal oedema [A] *	1/100 (1%)
Respiratory, thoracic and mediastinal disorders	
Dyspnoea [A] *	1/100 (1%)
Vascular disorders	
Ischaemia [A] *	1/100 (1%)

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA (11.0)

Other Adverse Events
Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	Rituximab + Chlorambucil
	Affected/At Risk (%)
Total	97/100 (97%)
Blood and lymphatic system disorders	
Anaemia [A] *	20/100 (20%)
Leukopenia [A] *	23/100 (23%)
Lymphopenia [A] *	41/100 (41%)
Neutropenia [A] *	41/100 (41%)
Thrombocytopenia [A] *	19/100 (19%)
Gastrointestinal disorders	
Abdominal pain [A] *	7/100 (7%)
Constipation [A] *	15/100 (15%)
Diarrhoea [A] *	19/100 (19%)
Dyspepsia [A] *	8/100 (8%)

	Rituximab + Chlorambucil
	Affected/At Risk (%)
Mouth ulceration [A] *	5/100 (5%)
Nausea [A] *	51/100 (51%)
Vomiting [A] *	22/100 (22%)
General disorders	
Chills [A] *	17/100 (17%)
Fatigue [A] *	31/100 (31%)
Infusion related reaction [A] *	5/100 (5%)
Mucosal inflammation [A] *	6/100 (6%)
Oedema peripheral [A] *	10/100 (10%)
Pyrexia [A] *	27/100 (27%)
Immune system disorders	
Hypersensitivity [A] *	5/100 (5%)
Infections and infestations	
Cellulitis [A] *	5/100 (5%)
Lower respiratory tract infection [A] *	11/100 (11%)
Nasopharyngitis [A] *	9/100 (9%)
Upper respiratory tract infection [A] *	16/100 (16%)
Urinary tract infection [A] *	5/100 (5%)
Metabolism and nutrition disorders	
Anorexia [A] *	7/100 (7%)
Hypokalaemia [A] *	5/100 (5%)
Hyponatraemia [A] *	6/100 (6%)
Hypophosphataemia [A] *	5/100 (5%)

	Rituximab + Chlorambucil
	Affected/At Risk (%)
Musculoskeletal and connective tissue disorders	
Arthralgia [A] *	9/100 (9%)
Back pain [A] *	12/100 (12%)
Pain in extremity [A] *	6/100 (6%)
Nervous system disorders	
Dizziness [A] *	15/100 (15%)
Headache [A] *	15/100 (15%)
Lethargy [A] *	7/100 (7%)
Paraesthesia [A] *	6/100 (6%)
Syncope [A] *	5/100 (5%)
Psychiatric disorders	
Insomnia [A] *	7/100 (7%)
Respiratory, thoracic and mediastinal disorders	
Cough [A] *	20/100 (20%)
Dyspnoea [A] *	13/100 (13%)
Pharyngolaryngeal pain [A] *	8/100 (8%)
Skin and subcutaneous tissue disorders	
Drug eruption [A] *	6/100 (6%)
Rash [A] *	13/100 (13%)
Vascular disorders	
Flushing [A] *	8/100 (8%)
Hypertension [A] *	6/100 (6%)
Hypotension [A] *	11/100 (11%)

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA (11.0)

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.

Results Point of Contact:

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