ClinicalTrials.gov Protocol and Results Registration System (PRS) Receipt
Release Date: 11/21/2014

ClinicalTrials.gov ID: NCT00472420

Study Identification

Unique Protocol ID:	ML20493
Brief Title:	A Study of MabThera (Rituximab) Plus Standard Chemotherapy in Patients With Previously Untreated Mantle Cell Lymphoma.
Official Title:	An Open-label Study of the Effect of the Addition of MabThera to Standard Chemotherapy on Clinical Response in Patients With Previously Untreated Mantle Cell Lymphoma
Secondary IDs:	

Study Status

Record Verification:	November 2014
Overall Status:	Completed
Study Start:	June 2007
Primary Completion:	May 2011 [Actual]
Study Completion:	May 2011 [Actual]

Sponsor/Collaborators

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

Oversight

FDA Regulated?:	No
IND/IDE Protocol?:	No

Review Board:	Approval Status: Approved Approval Number: 16464/07 Board Name: National Institute of Pharmacy Board Affiliation: Dept. of Clinical Trials Phone: +36 1 117 1488 Email: klinvizsg@ogyi.hu
Data Monitoring?:	
Plan to Share Data?:	
Oversight Authorities:	Hungary: Ministry of Health

Study Description

Brief Summary:	This single arm study will evaluate the benefit of adding MabThera to standard induction chemotherapy in patients with newly diagnosed mantle cell lymphoma. The safety and tolerability of a MabThera-containing first line regimen will also be assessed. All patients will receive MabThera (375mg/m2 iv) every 3 weeks for 8 cycles, in combination with standard chemotherapy. The anticipated time on study treatment is 3-12 months, and the target sample size is <100 individuals.
Detailed Description:	

Conditions

Conditions:	Mantle Cell Lymphoma
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:	Non-Randomized
Endpoint Classification:	Safety/Efficacy Study
Enrollment:	48 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: 1	Drug: rituximab [MabThera/Rituxan] 375mg/m2 iv every 3 weeks Drug: First line chemotherapy As prescribed

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age: 18 Years

Maximum Age:

Gender: Both

Accepts Healthy Volunteers?: No

Criteria: Inclusion Criteria:

- histologically-proven mantle cell lymphoma;
- previously untreated disease at stage II, III and IV, requiring therapy.

Exclusion Criteria:

- known hypersensitivity reaction to rituximab, or known anti-murine antibody reactivity or known hypersensitivity to murine antibodies;
- active malignancy other than mantle cell lymphoma within 5 years of start of study, with the exception of resected basal cell cancer, squamous cell cancer of the skin, or in situ cancer of the cervix;
- serious disorders interfering with full standard dosing chemotherapy;
- stage I disease.

Contacts/Locations

Study Officials: Clinical Trials
Study Director
Hoffmann-La Roche

Locations: Hungary
Kaposvar, Hungary, 7400

Szeged, Hungary, 6720

Zalaegerszeg, Hungary, 8901

Debrecen, Hungary, 4032

Gyor, Hungary, 9024

Miskolc, Hungary, 3529

Budapest, Hungary, 1122

References

Citations:

Links:

Study Data/Documents:

Study Results

Participant Flow

Reporting Groups

	Description
Rituximab Plus (+) Chemotherapy	Participants received rituximab, 375 milligrams per square meter (mg/m^2), intravenously (IV), on Day 1 of Cycles 1-8 (21-day cycle). Participants also received 1 of the following chemotherapies: CHOP, Cycles 1-8: cyclophosphamide, 750 mg/m^2, IV, doxorubicin, 50 mg/m^2, IV, or epirubicin, 70 mg/m^2, IV, vincristine, 1.4 mg/m^2, IV, on Day 1 of Cycles 1-8, and methylprednisolone, 16 mg/d, IV or orally (PO), on Days 1-5. OR Hyper-CVAD/M-A, Cycles 1, 3, 5, and 7: cyclophosphamide, 300 mg/m^2, IV, every 12 hours (q12h) on Days 2-4; mesna, 600 mg/m^2, IV, 1 hour before the start of cyclophosphamide on Days 2-4; doxorubicin, 50 mg/m^2, IV, or epirubicin, 70 mg/m^2, IV, on Day 5; vincristine, 1.4 mg/m^2, IV, on Days 5 and 12; and dexamethasone, IV or PO, 40 mg/day on Days 2-5 and Days 12-15. Hyper-CVAD/M-A, Cycles 2, 4, 6, and 8: methotrexate, 200 mg/m^2, IV, followed by 800 mg/m^2, IV, on Day 2; cytarabine, 3000 mg/m^2, IV over 2 hours, q12h on Day 3 (2 doses) or Days 3-4 (4 doses).

Induction Treatment Period

	Rituximab Plus (+) Chemotherapy
Started	48
Completed	32
Not Completed	16
Physician Decision	9
Adverse Event	3
Non-compliance	1
Death	3

Follow-up Period

	Rituximab Plus (+) Chemotherapy
Started	32
Completed	15
Not Completed	17
Death	5
Physician Decision	9
Lost to Follow-up	2
Protocol Violation	1

Baseline Characteristics

Analysis Population Description

Intent-to-treat (ITT) population: all randomized participants who received at least 1 dose of study treatment.

Reporting Groups

	Description
Rituximab + Chemotherapy	Participants received rituximab, 375 mg/m^2, IV, on Day 1 of Cycles 1-8 (21-day cycle). Participants also received 1 of the following chemotherapies: CHOP, Cycles 1-8: cyclophosphamide, 750 mg/m^2, IV, doxorubicin, 50 mg/m^2, IV, or epirubicin, 70 mg/m^2, IV, vincristine, 1.4 mg/m^2, IV, on Day 1 of Cycles 1-8, and methylprednisolone, 16 mg/d, IV or PO, on Days 1-5. OR Hyper-CVAD/M-A, Cycles 1, 3, 5, and 7: cyclophosphamide, 300 mg/m^2, IV, q12h on Days 2-4; mesna, 600 mg/m^2, IV, 1 hour before the start of cyclophosphamide on Days 2-4; doxorubicin, 50 mg/m^2, IV, or epirubicin, 70 mg/m^2, IV, on Day 5; vincristine, 1.4 mg/m^2, IV, on Days 5 and 12; and dexamethasone, IV or PO, 40 mg/day on Days 2-5 and Days 12-15. Hyper-CVAD/M-A, Cycles 2, 4, 6, and 8: methotrexate, 200 mg/m^2, IV, followed by 800 mg/m^2, IV, on Day 2; cytarabine, 3000 mg/m^2, IV over 2 hours, q12h on Day 3 (2 doses) or Days 3-4 (4 doses).

Baseline Measures

	Rituximab + Chemotherapy
Number of Participants	48
Age, Continuous [1] [units: years] Median (Full Range)	70.20 (44.46 to 82.31)
Gender, Male/Female [units: participants]	
Female	16
Male	32

[1] 47 participants were included in the calculation of age.

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Number of Participants Achieving Complete Remission (CR) (Including Unconfirmed CR [CR(u)]) or Partial Remission (PR)

Measure Description	CR was defined by: a) disappearance of clinical/radiographic evidence of disease, disease-related symptoms, and biochemical abnormalities; b) decrease in lymph nodes (LNs) greater than (>) 1.5 centimeters (cm) in greatest transverse diameter (GTD) to less than (<) 1.5 cm, a decrease in LNs 1.1 - 1.5 cm to 1 cm or 75 percent (%) decrease in sum of the products of GTD (SPD); c) non-palpable spleen, decreased size of enlarged organs, and disappearance of nodules; and d) disappearance of bone marrow (BM) infiltrate. CR(u) was defined as fulfilling a) and c), above, with greater than or equal to (≥) 1 of the following: a) > 75% decrease in SPD of LNs > 1.5 cm, and > 75% decrease in SPD of previously confluent LNs; b) indeterminate BM, or c) confirmed CR. PR was defined by: a) 50% decrease in SPD of the 6 largest LNs; b) no increase in LNs, liver, or spleen size; c) ≥ 50% decrease in splenic and hepatic nodule SPDs; d) no measurable disease in other organs; and e) no new sites of disease.
Time Frame	Screening, Baseline (BL), every 21 days thereafter up to Week 27, every 3 months thereafter up to Month 24, Withdrawal Visit (4 weeks after discontinuation of study treatment)
Safety Issue?	No

Analysis Population Description

ITT population

Reporting Groups

	Description
Rituximab + Chemotherapy	Participants received rituximab, 375 mg/m^2, IV, on Day 1 of Cycles 1-8 (21-day cycle). Participants also received 1 of the following chemotherapies: CHOP, Cycles 1-8: cyclophosphamide, 750 mg/m^2, IV, doxorubicin, 50 mg/m^2, IV, or epirubicin, 70 mg/m^2, IV, vincristine, 1.4 mg/m^2, IV, on Day 1 of Cycles 1-8, and methylprednisolone, 16 mg/d, IV or PO, on Days 1-5. OR Hyper-CVAD/M-A, Cycles 1, 3, 5, and 7: cyclophosphamide, 300 mg/m^2, IV, q12h on Days 2-4; mesna, 600 mg/m^2, IV, 1 hour before the start of cyclophosphamide on Days 2-4; doxorubicin, 50 mg/m^2, IV, or epirubicin, 70 mg/m^2, IV, on Day 5; vincristine, 1.4 mg/m^2, IV, on Days 5 and 12; and dexamethasone, IV or PO, 40 mg/day on Days 2-5 and Days 12-15. Hyper-CVAD/M-A, Cycles 2, 4, 6, and 8: methotrexate, 200 mg/m^2, IV, followed by 800 mg/m^2, IV, on Day 2; cytarabine, 3000 mg/m^2, IV over 2 hours, q12h on Day 3 (2 doses) or Days 3-4 (4 doses).

Measured Values

	Rituximab + Chemotherapy
Number of Participants Analyzed	48
Number of Participants Achieving Complete Remission (CR) (Including Unconfirmed CR [CR(u)]) or Partial Remission (PR) [units: participants]	
CR	19

	Rituximab + Chemotherapy
PR	8

2. Secondary Outcome Measure:

Measure Title	Progression Free Survival (PFS)
Measure Description	PFS was defined as the median time, in months, from the date of study entry to disease progression, death due to mantle cell lymphoma, or last contact. Progressive disease (PD) was defined by: a) 50% increase from nadir in the SPD of any previously identified abnormal LN, or b) appearance of any new lesion during or at the end of treatment. The 95% confidence interval (CI) was estimated using Kaplan-Meier methodology.
Time Frame	Screening, BL, every 21 days thereafter up to Week 27, every 3 months thereafter up to Month 24, Withdrawal Visit (4 weeks after discontinuation of study treatment)
Safety Issue?	No

Analysis Population Description

ITT population

Reporting Groups

	Description
Rituximab + Chemotherapy	Participants received rituximab, 375 mg/m^2, IV, on Day 1 of Cycles 1-8 (21-day cycle). Participants also received 1 of the following chemotherapies: CHOP, Cycles 1-8: cyclophosphamide, 750 mg/m^2, IV, doxorubicin, 50 mg/m^2, IV, or epirubicin, 70 mg/m^2, IV, vincristine, 1.4 mg/m^2, IV, on Day 1 of Cycles 1-8, and methylprednisolone, 16 mg/d, IV or PO, on Days 1-5. OR Hyper-CVAD/M-A, Cycles 1, 3, 5, and 7: cyclophosphamide, 300 mg/m^2, IV, q12h on Days 2-4; mesna, 600 mg/m^2, IV, 1 hour before the start of cyclophosphamide on Days 2-4; doxorubicin, 50 mg/m^2, IV, or epirubicin, 70 mg/m^2, IV, on Day 5; vincristine, 1.4 mg/m^2, IV, on Days 5 and 12; and dexamethasone, IV or PO, 40 mg/day on Days 2-5 and Days 12-15. Hyper-CVAD/M-A, Cycles 2, 4, 6, and 8: methotrexate, 200 mg/m^2, IV, followed by 800 mg/m^2, IV, on Day 2; cytarabine, 3000 mg/m^2, IV over 2 hours, q12h on Day 3 (2 doses) or Days 3-4 (4 doses).

Measured Values

	Rituximab + Chemotherapy
Number of Participants Analyzed	48
Progression Free Survival (PFS) [units: months]	30.456 (19.011 to 41.901)

	Rituximab + Chemotherapy
Median (95% Confidence Interval)	

3. Secondary Outcome Measure:

Measure Title	Event Free Survival (EFS)
Measure Description	EFS was defined as the median time, in months, from the date of study entry disease progression, relapse, secondary malignancy, death or last contact. Relapse was defined by: a) appearance of any new lesion or a ≥ 50% increase in size of previously involved sites, or b) ≥ 50% increase in GTD of any previously identified LN >1 cm in short axis or in the SPD of more than one LN. The 95% CI was estimated using Kaplan-Meier methodology.
Time Frame	Screening, BL, every 21 days thereafter up to Week 27, every 3 months thereafter up to Month 24, Withdrawal Visit (4 weeks after discontinuation of study treatment)
Safety Issue?	No

Analysis Population Description

ITT population

Reporting Groups

	Description
Rituximab + Chemotherapy	Participants received rituximab, 375 mg/m^2, IV, on Day 1 of Cycles 1-8 (21-day cycle). Participants also received 1 of the following chemotherapies: CHOP, Cycles 1-8: cyclophosphamide, 750 mg/m^2, IV, doxorubicin, 50 mg/m^2, IV, or epirubicin, 70 mg/m^2, IV, vincristine, 1.4 mg/m^2, IV, on Day 1 of Cycles 1-8, and methylprednisolone, 16 mg/d, IV or PO, on Days 1-5. OR Hyper-CVAD/M-A, Cycles 1, 3, 5, and 7: cyclophosphamide, 300 mg/m^2, IV, q12h on Days 2-4; mesna, 600 mg/m^2, IV, 1 hour before the start of cyclophosphamide on Days 2-4; doxorubicin, 50 mg/m^2, IV, or epirubicin, 70 mg/m^2, IV, on Day 5; vincristine, 1.4 mg/m^2, IV, on Days 5 and 12; and dexamethasone, IV or PO, 40 mg/day on Days 2-5 and Days 12-15. Hyper-CVAD/M-A, Cycles 2, 4, 6, and 8: methotrexate, 200 mg/m^2, IV, followed by 800 mg/m^2, IV, on Day 2; cytarabine, 3000 mg/m^2, IV over 2 hours, q12h on Day 3 (2 doses) or Days 3-4 (4 doses).

Measured Values

	Rituximab + Chemotherapy
Number of Participants Analyzed	48
Event Free Survival (EFS) [units: months]	40.049 (33.296 to 46.802)

	Rituximab + Chemotherapy
Median (95% Confidence Interval)	

Reported Adverse Events

Time Frame	Adverse events (AEs) were recorded throughout the study up to 3 months after the last study drug administration.
Additional Description	All participants who received at least 1 dose of study treatment were included in the safety analysis.

Reporting Groups

	Description
Rituximab + Chemotherapy	Participants received rituximab, 375 mg/m^2, IV, on Day 1 of Cycles 1-8 (21-day cycle). Participants also received 1 of the following chemotherapies: CHOP, Cycles 1-8: cyclophosphamide, 750 mg/m^2, IV, doxorubicin, 50 mg/m^2, IV, or epirubicin, 70 mg/m^2, IV, vincristine, 1.4 mg/m^2, IV, on Day 1 of Cycles 1-8, and methylprednisolone, 16 mg/d, IV or PO, on Days 1-5. OR Hyper-CVAD/M-A, Cycles 1, 3, 5, and 7: cyclophosphamide, 300 mg/m^2, IV, q12h on Days 2-4; mesna, 600 mg/m^2, IV, 1 hour before the start of cyclophosphamide on Days 2-4; doxorubicin, 50 mg/m^2, IV, or epirubicin, 70 mg/m^2, IV, on Day 5; vincristine, 1.4 mg/m^2, IV, on Days 5 and 12; and dexamethasone, IV or PO, 40 mg/day on Days 2-5 and Days 12-15. Hyper-CVAD/M-A, Cycles 2, 4, 6, and 8: methotrexate, 200 mg/m^2, IV, followed by 800 mg/m^2, IV, on Day 2; cytarabine, 3000 mg/m^2, IV over 2 hours, q12h on Day 3 (2 doses) or Days 3-4 (4 doses).

Serious Adverse Events

	Rituximab + Chemotherapy
	Affected/At Risk (%)
Total	25/48 (52.08%)
Blood and lymphatic system disorders	
Agranulocytosis [A] *	4/48 (8.33%)
Anaemia [A] *	6/48 (12.5%)
Bone marrow failure [A] *	1/48 (2.08%)

	Rituximab + Chemotherapy
	Affected/At Risk (%)
Febrile neutropenia [A] *	3/48 (6.25%)
Granulocytopenia [A] *	1/48 (2.08%)
Neutropenia [A] *	1/48 (2.08%)
Pancytopenia [A] *	4/48 (8.33%)
Thrombocytopenia [A] *	4/48 (8.33%)
Cardiac disorders	
Acute coronaria syndrome [A] *	1/48 (2.08%)
Arrythmia [A] *	1/48 (2.08%)
Atrial fibrillation [A] *	1/48 (2.08%)
Heart injury [A] *	1/48 (2.08%)
Ventricular tachycardia [A] *	1/48 (2.08%)
Gastrointestinal disorders	
Diarrhoea [A] *	1/48 (2.08%)
Nausea [A] *	1/48 (2.08%)
General disorders	
Disease recurrence [A] *	1/48 (2.08%)
Pyrexia [A] *	3/48 (6.25%)
Infections and infestations	
Encephalomalacia [A] *	1/48 (2.08%)
Periproctal abscess [A] *	1/48 (2.08%)
Pneumonia [A] *	4/48 (8.33%)
Sepsis [A] *	2/48 (4.17%)
Septic shock [A] *	1/48 (2.08%)

	Rituximab + Chemotherapy
	Affected/At Risk (%)
Sinusitis [A] *	1/48 (2.08%)
Metabolism and nutrition disorders	
Hyperglycaemia [A] *	2/48 (4.17%)
Musculoskeletal and connective tissue disorders	
Muscular weakness [A] *	1/48 (2.08%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	
Progression of pre-existing cancer [A] *	1/48 (2.08%)
Nervous system disorders	
Transient ischaemic attack [A] *	1/48 (2.08%)
Renal and urinary disorders	
Renal failure acute [A] *	1/48 (2.08%)
Respiratory, thoracic and mediastinal disorders	
Bronchospasm [A] *	1/48 (2.08%)
Pleurlopneumonia [A] *	1/48 (2.08%)
Pneumothorax [A] *	1/48 (2.08%)
Respiratory failure [A] *	1/48 (2.08%)
Skin and subcutaneous tissue disorders	
Urticaria, perioral tingling [A] *	1/48 (2.08%)
Surgical and medical procedures	
Tumour excision [A] *	1/48 (2.08%)
Vascular disorders	
Deep vein thrombosis [A] *	2/48 (4.17%)
Haemorrhage [A] *	1/48 (2.08%)

	Rituximab + Chemotherapy
	Affected/At Risk (%)
Hypertensive crisis [A] *	1/48 (2.08%)

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, CTCAE (2.0)

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

	Rituximab + Chemotherapy
	Affected/At Risk (%)
Total	23/48 (47.92%)
Blood and lymphatic system disorders	
Agranulocytosis [A] *	5/48 (10.42%)
Anaemia [A] *	1/48 (2.08%)
Bacteremia [A] *	1/48 (2.08%)
Bone marrow toxicity [A] *	1/48 (2.08%)
Febrile neutropenia [A] *	1/48 (2.08%)
Neutropenia [A] *	1/48 (2.08%)
Pancytopenia [A] *	2/48 (4.17%)
Thrombocytopenia [A] *	4/48 (8.33%)
Cardiac disorders	
Carotid sinus syndrome [A] *	1/48 (2.08%)
Eye disorders	
Ulcus corneae [A] *	1/48 (2.08%)
Gastrointestinal disorders	
Choking sensation [A] *	1/48 (2.08%)
Diarrhoea [A] *	2/48 (4.17%)

	Rituximab + Chemotherapy
	Affected/At Risk (%)
Diarrhoea infectious [A] *	1/48 (2.08%)
Nausea [A] *	1/48 (2.08%)
General disorders	
Chilliness [A] *	1/48 (2.08%)
Chills [A] *	4/48 (8.33%)
Pain [A] *	1/48 (2.08%)
Pyrexia [A] *	3/48 (6.25%)
Hepatobiliary disorders	
Hepatic function abnormal [A] *	1/48 (2.08%)
Infections and infestations	
Gastroenteritis [A] *	1/48 (2.08%)
Helicobacter test positive [A] *	1/48 (2.08%)
Herpes labialis [A] *	1/48 (2.08%)
Herpes zoster [A] *	1/48 (2.08%)
Oral thrush [A] *	1/48 (2.08%)
Pneumonia [A] *	2/48 (4.17%)
Prostatitis [A] *	1/48 (2.08%)
Upper respiratory tract infection [A] *	1/48 (2.08%)
Injury, poisoning and procedural complications	
Patella fracture [A] *	1/48 (2.08%)
Renal and urinary disorders	
Renal failure [A] *	1/48 (2.08%)
Respiratory, thoracic and mediastinal disorders	

	Rituximab + Chemotherapy
	Affected/At Risk (%)
Hydrothorax [A] *	1/48 (2.08%)
Skin and subcutaneous tissue disorders	
Pruritus cutaneous [A] *	1/48 (2.08%)
Toxic skin eruption [A] *	1/48 (2.08%)
Toxicoderma [A] *	1/48 (2.08%)
Vascular disorders	
Thrombophlebitis [A] *	1/48 (2.08%)

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, CTCAE (2.0)

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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