SUPPLEMENTARY APPENDIX

Efficacy and safety assessment of prolonged maintenance with subcutaneous rituximab in patients with relapsed or refractory indolent non-Hodgkin lymphoma: results of the phase III MabCute study

Simon Rule,[1] Wolney Gois Barreto,[2] Javier Briones,[3] Angelo M. Carella,[4] Olivier Casasnovas,[5] Chris Pocock,[6] Clemens-Martin Wendtner,[7] Francesco Zaja,[8] Susan Robson,[9] Lachlan MacGregor,[9] Roger R. Tschopp,[9] Sonja Nick[9] and Martin Dreyling[10]

[1]Derriford Hospital and Plymouth University Medical School, Plymouth, UK; [2]Hemocentro Ribeirão Preto, University of São Paulo, São Paulo, Brazil; [3]Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; [4]IRCCS AOU San Martino-IST, Genova, Italy; [5]Centre Hospitalier Universitaire François Mitterand, Dijon, France; [6]Kent & Canterbury Hospital, Canterbury, UK; [7]Munich Clinic Schwabing, Academic Teaching Hospital, Ludwig-Maximilians University, Munich, Germany; [8]DSM, University of Trieste, Trieste, Italy; [9]F. Hoffmann-La Roche Ltd, Basel, Switzerland and [10]Klinikum der Universität München, Munich, Germany

 doi:10.3324/haematol.2020.274803

Received: November 10, 2020.

Accepted: May 3, 2021.

Pre-published: June 17, 2021.

Correspondence: *MARTIN DREYLING* - martin.dreyling@med.uni-muenchen.de

Online Supplementary Appendix

Study treatments

Rituximab was given intravenously at a dose of 375 mg/m^2 body surface area as a single infusion at the beginning of Induction, and subsequently subcutaneously at a fixed dose of 1400 mg as a single injection per cycle (Induction, Maintenance I and Maintenance II).

At Induction, rituximab (intravenous [IV] or subcutaneous [SC]) was followed by 6 to 8 cycles of chemotherapy, which was selected at the investigator's discretion for each patient, as follows:

- bendamustine (6 cycles);
- cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) (6 cycles);
- cyclophosphamide, vincristine and prednisone (CVP) (8 cycles);
- fludarabine, cyclophosphamide and mitoxantrone (FCM) (6 cycles);
- mitoxantrone, chlorambucil and prednisone (MCP);
- cyclophosphamide, doxorubicin, vincristine and prednisone with interferon alfa-2b (CHVP-IFN) (6 cycles);
- Chlorambucil (8 cycles);
- any fludarabine-containing regimen including oral fludarabine (6 cycles);
- gemcitabine, ifosfamide and oxaliplatin (GIFOX) (6 cycles).

Rituximab was given before chemotherapy (with the exception of the corticosteroid component).

During Induction (6 to 8 months' duration), study treatment consisted of one cycle of rituximab IV followed by seven cycles rituximab SC in patients without infusion- or administration-related reactions (IRRs/ARRs) followed by a chemotherapy as described above. Patients not able to receive their first full dose of rituximab IV in cycle 1 because of a grade 3 or 4 IRR or ARR (according to the National Cancer Institute Common Terminology) received their second rituximab dose intravenously in cycle 2 and their third rituximab dose subcutaneously in cycle 3 if the second infusion was not associated with a grade 3 or 4 IRR or

ARR. Patients with a grade 3 or 4 IRR/ARR after the second IV rituximab dose were withdrawn from the study.

During the initial maintenance period (Maintenance I; 24 months' duration), patients received 12 cycles of rituximab SC as a single 1400 mg injection every 8 weeks for up to 2 years. Therapy was to start within 8 to 12 weeks of the last rituximab induction dose.

For prolonged maintenance (Maintenance II; minimum 15 months' duration), patients who had completed Induction and Maintenance I and were who were considered responders (partial or complete response; PR or CR) after Maintenance I were randomized 1:1 to Maintenance II, during which they received (i) rituximab SC as a single 1400 mg injection every 8 weeks for up to 2 years unless they withdrew because of disease progression, unacceptable toxicity or withdrawal of patient consent, or (ii) observation with no further treatment.

Assessments at baseline

Confirmation and documentation of adequate non-Hodgkin lymphoma (NHL) diagnosis, staging and CD20 expression were obtained from the patient's history and medical records. Ann Arbor disease staging was performed and bone marrow assessment carried out to determine baseline bone marrow involvement. Assessments were also required to confirm suspected CR in patients with bone marrow involvement at baseline.

Tumor assessments

Tumors were assessed and current disease staged by computed tomography scan with contrast or by other means for lymphomas not detectable radiographically. Follicular Lymphoma International Prognostic Index (FLIPI) scores and Eastern Cooperative Oncology Group (ECOG) performance status were also assessed.

Sample size

The sample size was based on assumed median PFS from time of randomization in patients randomized to extended maintenance with rituximab SC or observation in Maintenance II (PFS_{rand}) of 38 and 23 months in the rituximab and observation arms,

respectively. On this basis, 129 PFS_{rand} events were needed for 80% power at 5% significance to detect a target effect HR of 0.605, with approximately 700 patients needed initially to yield the 330 required for randomization.

Note on adverse event recording

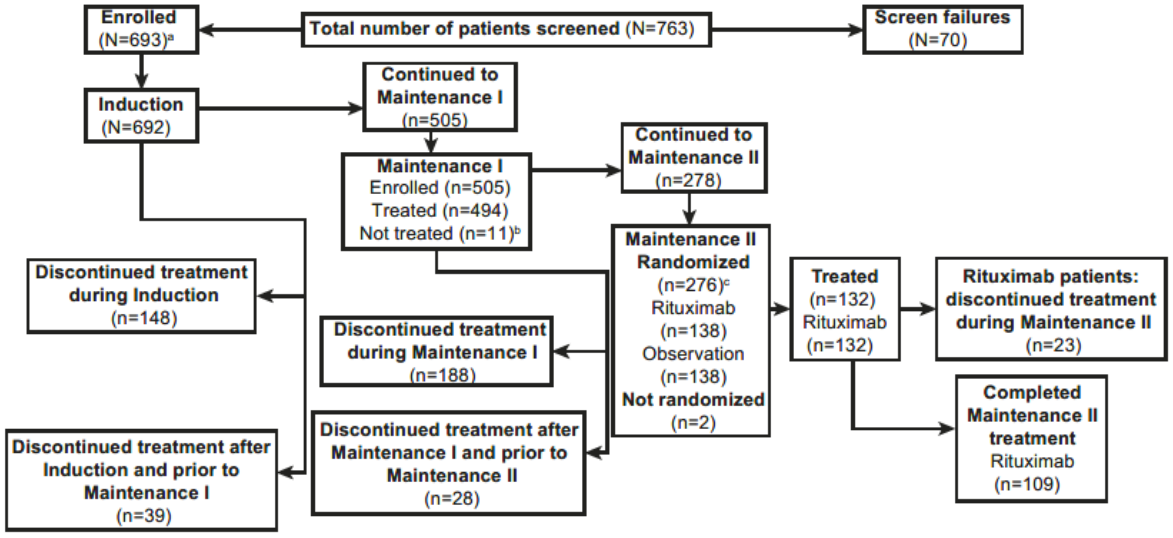
Reporting periods for non-serious grade 1 or 2 adverse events (AEs) in Maintenance II were dependent on time from last dose; thus, a longer period was available for AE capture from rituximab patients than from those randomized to observation. We note also that an inconsistency in wording of the protocol (subsequently corrected) led to cessation of reporting of AEs in observation patients 28 days after randomization. To enable consistent reporting of events in both arms, the protocol was updated so that AEs of grade ≥3 were reported up to 6 months after the last dose in the rituximab arm or last visit in the observation arm, or to end of study (EOS; or start of new anti-lymphoma treatment for unrelated AEs or serious adverse events [SAEs]), whichever came first. As a result of this change, all AEs were reported retrospectively.

Monitoring and steering committees

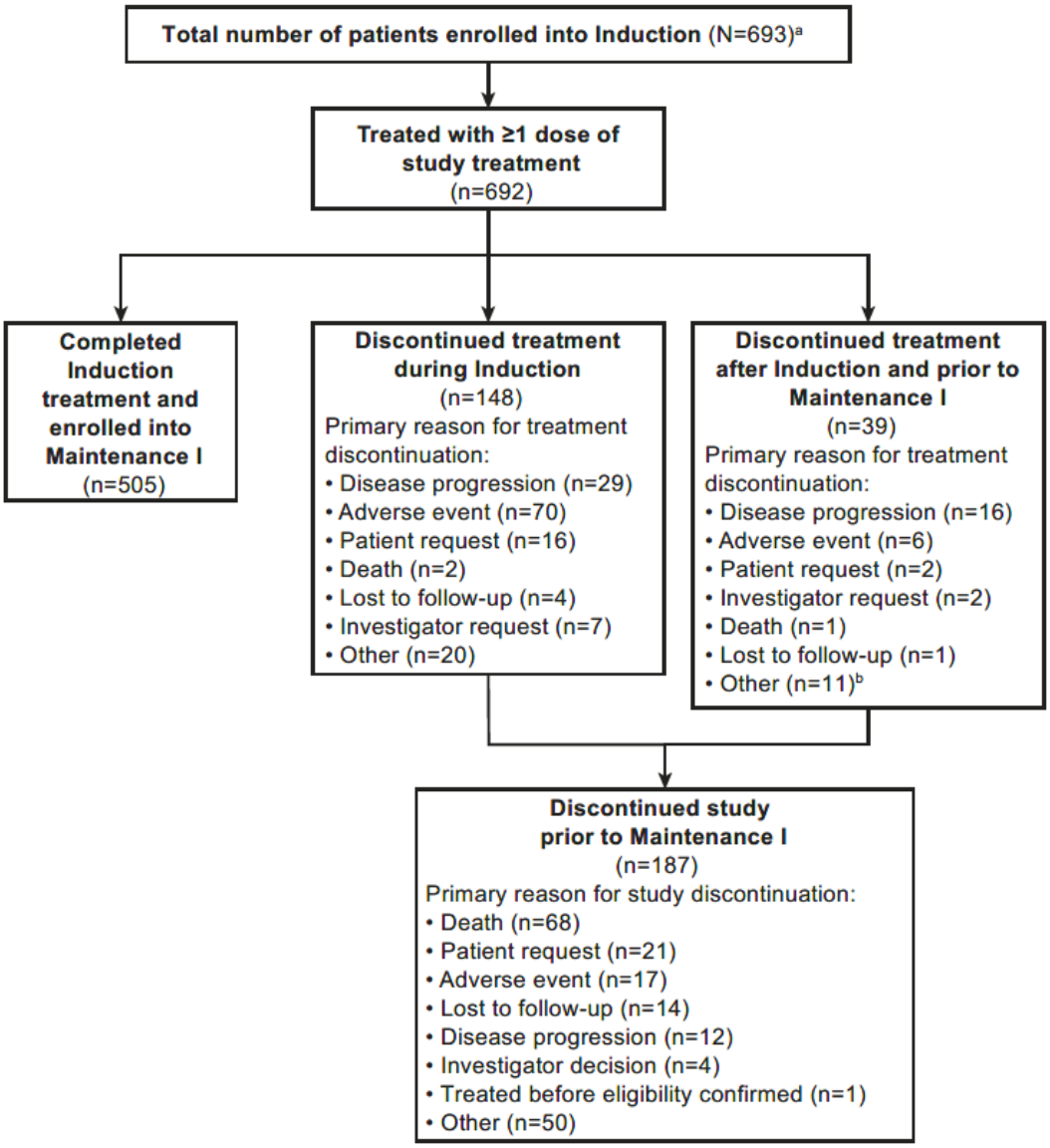
An independent Data Monitoring Committee (iDMC) was established to monitor safety and study conduct. A steering committee consisting of seven expert hematologists and two representatives from the study sponsor was also established to provide scientific and medical guidance.

Supplementary Figure S1. Patient disposition: all study phases (A); Induction (B); and Maintenance I (C).

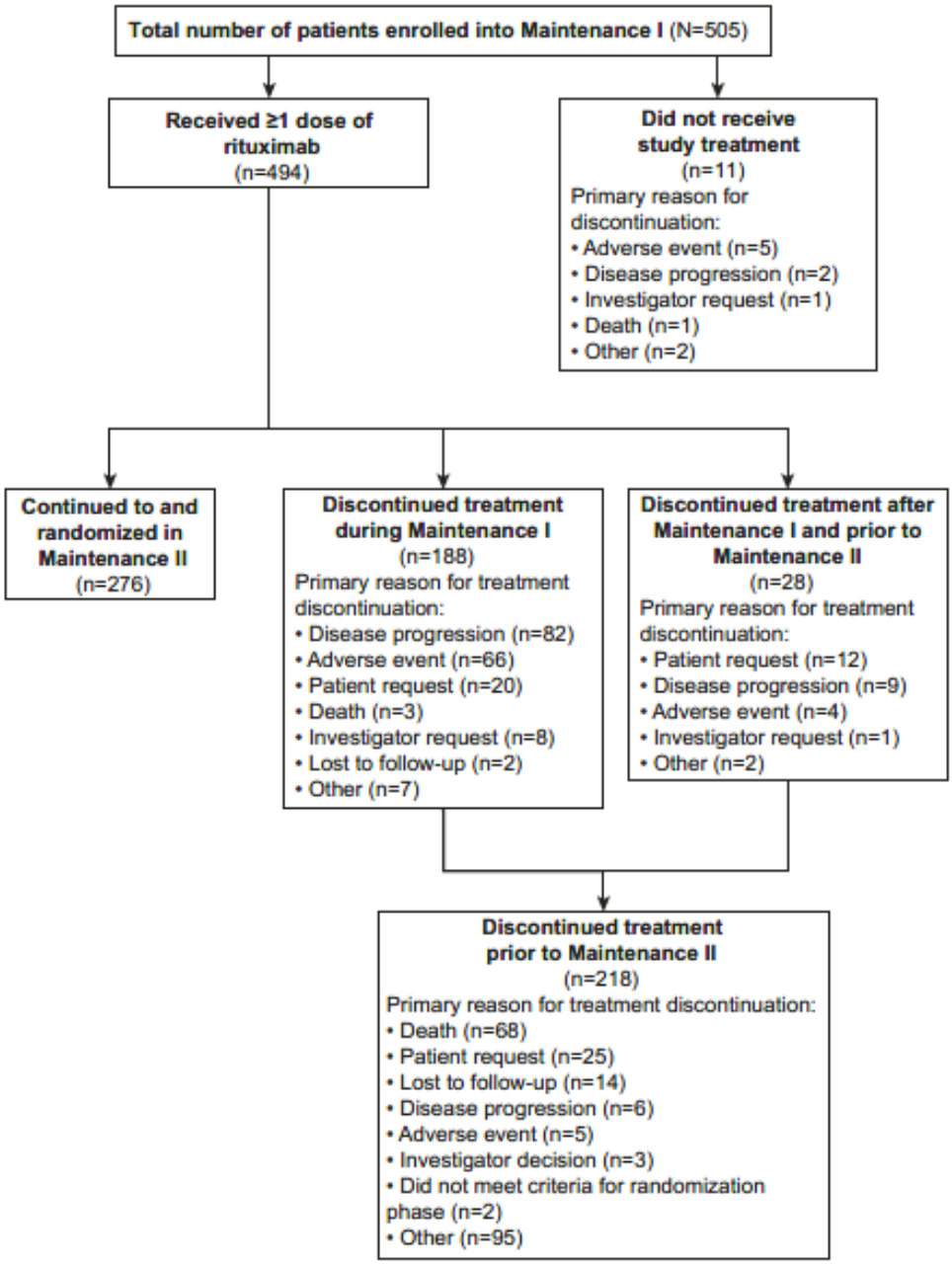
A



B


Total number of patients enrolled into Induction (N=693)[a]
Treated with ≥1 dose of study treatment (n=692)
Completed Induction treatment and enrolled into Maintenance I (n=505)
Discontinued treatment during Induction (n=148)
Primary reason for treatment discontinuation:
• Disease progression (n=29)
• Adverse event (n=70)
• Patient request (n=16)
• Death (n=2)
• Lost to follow-up (n=4)
• Investigator request (n=7)
• Other (n=20)
Discontinued treatment after Induction and prior to Maintenance I (n=39)
Primary reason for treatment discontinuation:
• Disease progression (n=16)
• Adverse event (n=6)
• Patient request (n=2)
• Investigator request (n=2)
• Death (n=1)
• Lost to follow-up (n=1)
• Other (n=11)[b]
Discontinued study prior to Maintenance I (n=187)
Primary reason for study discontinuation:
• Death (n=68)
• Patient request (n=21)
• Adverse event (n=17)
• Lost to follow-up (n=14)
• Disease progression (n=12)
• Investigator decision (n=4)
• Treated before eligibility confirmed (n=1)
• Other (n=50)

C



[a]One patient was enrolled but did not participate in Induction (failed screening).

[b]Eleven patients discontinued treatment after Induction and before Maintenance I for other reasons (all had stable disease).

[c]Two patients initially planned for randomization failed to satisfy the criteria for continuing treatment and were therefore not in fact treated In Maintenance II.

Supplementary Table S1. Chemotherapy regimens used during Induction, and number (%) of patients remaining in each study phase.

Induction chemotherapy	Induction (N=692)[a]	Maintenance I (N=494)	Maintenance II		
			Rituximab (N=138)	Observation (N=138)	Total (N=276)
Bendamustine	419 (60.5)	302 (61.1)	80 (58.0)	79 (57.2)	159 (57.6)
CHOP	86 (12.4)	67 (13.6)	20 (14.5)	19 (13.8)	39 (14.1)
CVP	82 (11.8)	66 (13.4)	26 (18.8)	22 (15.9)	48 (17.4)
FCM	14 (2.0)	8 (1.6)	2 (1.4)	2 (1.4)	4 (1.4)
MCP	7 (1.0)	5 (1.0)	1 (0.7)	3 (2.2	4 (1.4)
Chlorambucil	32 (4.6)	21 (4.3)	6 (4.3)	5 (3.6)	11 (4.0)
Other fludarabine-containing regimen	51 (7.4)	25 (5.1)	3 (2.2)	8 (5.8)	11 (4.0)

CHOP:cyclophosphamide, doxorubicin, vincristine and prednisone; CVP: cyclophosphamide, vincristine and prednisone; FCM: fludarabine, cyclophosphamide and mitoxantrone; MCP: mitoxantrone, chlorambucil and prednisone.

[a]One patient received rituximab but no chemotherapy.

Supplementary Table S2. Patient disposition by induction chemotherapy from Induction to Maintenance I.

Category	Number of patients (%)				
	Benda (N=419)	**CHOP (N=86)**	**CVP (N=82)**	**Other (N=105)[a]**	**Total (N=692)**
Completed 8 cycles of rituximab during Induction	318 (75.9)	71 (82.6)	71 (86.6)	64 (61.0)	524 (75.7)
Discontinued study treatment during Induction	87 (20.8)	14 (16.3)	11 (13.4)	36 (34.3)	148 (21.4)
Primary reason for discontinuing study treatment during Induction					
Disease progression	15 (3.6)	4 (4.7)	3 (3.7)	7 (6.7)	29 (4.2)
Adverse event	42 (10.0)	5 (5.8)	4 (4.9)	19 (18.1)	70 (10.1)
Patient request	10 (2.4)	3 (3.5)	2 (2.4)	1 (1.0)	16 (2.3)
Death	2 (0.5)	0	0	0	2 (0.3)
Investigator request	3 (0.7)	0	2 (2.4)	2 (1.9)	7 (1.0)
Lost to follow-up	3 (0.7)	0	0	1 (1.0)	4 (0.6)
Other	12 (2.9)	2 (2.3)	0	6 (5.7)	20 (2.9)
Discontinued study treatment after Induction and before Maintenance I	23 (5.5)	3 (3.5)	4 (4.9)	9 (8.6)	39 (5.6)
Primary reason for discontinuing study treatment after Induction and before Maintenance I					
Disease progression	8 (1.9)	2 (2.3)	2 (2.4)	4 (3.8)	16 (2.3)
Adverse event	4 (1.0)	0	0	2 (1.9)	6 (0.9)
Patient request	2 (0.5)	0	0	0	2 (0.3)
Death	1 (0.2)	0	0	0	1 (0.1)
Investigator request	2 (0.5)	0	0	0	2 (0.3)
Lost to follow-up	1 (0.2)	0	0	0	1 (0.1)
Other	5 (1.2)	1 (1.2)	2 (2.4)	3 (2.9)	11 (1.6)
Discontinued study before Maintenance I	110 (26.3)	17 (19.8)	15 (18.3)	45 (42.9)	187 (27.0)
Primary reason for discontinuing study before Maintenance I					

Treated before eligibility confirmed	1 (0.2)	0	0	0	1 (0.1)
Disease progression	3 (0.7)	3 (3.5)	3 (3.7)	3 (2.9)	12 (1.7)
Adverse event	12 (2.9)	2 (2.3)	0	3 (2.9)	17 (2.5)
Patient request	15 (3.6)	2 (2.3)	3 (3.7)	1 (1.0)	21 (3.0)
Death	41 (9.8)	6 (7.0)	1 (1.2)	20 (19.0)	68 (9.8)
Investigator decision	3 (0.7)	0	1 (1.2)	0	4 (0.6)
Lost to follow-up	10 (2.4)	1 (1.2)	1 (1.2)	2 (1.9)	14 (2.0)
Other	25 (6.0)	3 (3.5)	6 (7.3)	16 (15.2)	50 (7.2)

Benda: bendamustine; CHOP: cyclophosphamide, doxorubicin, vincristine and prednisone; CVP: cyclophosphamide, vincristine and prednisone.

[a]Included fludarabine, cyclophosphamide and mitoxantrone (FCM), mitoxantrone, chlorambucil and prednisone (MCP), chlorambucil, or other fludarabine-containing regimen.

Supplementary Table S3. Patient and disease characteristics at screening/baseline according to induction chemotherapy received for the three most frequently administered regimens.

Characteristic	Benda n=419	CHOP n=86	CVP n=82
Median age, years (range)	66 (38–88)	62 (20–82)	63 (36–89)
Male, n (%)	211 (50.4)	45 (52.3)	37 (45.1)
Ann Arbor stage at screening, n (%)	n=398	n=86	n=81
I	19 (4.8)	5 (5.8)	12 (14.8)
II	47 (11.8)	6 (7.0)	7 (8.6)
III	93 (23.4)	17 (19.8)	21(25.9)
IV	239 (60.1)	58 (67.4)	41 (50.6)
FLIPI score, n (%)*	n=249	n=54	n=43
Low	70 (28.1)	16 (29.6)	13 (30.2)
Intermediate	75 (30.1)	18 (33.3)	15 (34.9)
High	102 (41.0)	20 (37.0)	15 (34.9)
Not done	2 (0.8)	0	0
Bone marrow involvement, n/N (%)	179/357 (50.1)	38/72 (52.8)	35/67 (52.2)
Type of NHL at screening, n (%)			
FL	249 (59.4)	54 (62.8)	43 (52.4)
WM/LPL	72 (17.2)	13 (15.1)	12 (14.6)
MZL	84 (20.0)	14 (16.3)	25 (30.5)

*FL patients only.

Benda:bendamustine; CHOP: cyclophosphamide, doxorubicin, vincristine and prednisone; CVP: cyclophosphamide, vincristine and prednisone; FL: follicular lymphoma; FLIPI: Follicular Lymphoma International Prognostic Index; MZL: marginal zone lymphoma; NHL: non-Hodgkin lymphoma; WM/LPL: Waldenström macroglobulinemia/lymphoplasmacytic lymphoma.

Supplementary Table S4. Number (%) of TEAEs during Induction for the three most frequently administered chemotherapy regimens in the safety population. Events seen in ≥5% of patients in any of the listed treatment groups.

Category	Benda (N=419)	CHOP (N=86)	CVP (N=82)
Total no. of patients with ≥1 TEAE	381 (90.9)	74 (86.0)	66 (80.5)
General disorders and administration site conditions	**254 (60.6)**	**34 (39.5)**	**34 (41.5)**
Pyrexia	87 (20.8)	7 (8.1)	8 (9.8)
Asthenia	70 (16.7)	5 (5.8)	3 (3.7)
Fatigue	59 (14.1)	13 (15.1)	9 (11.0)
Chills	32 (7.6)	1 (1.2)	5 (6.1)
Gastrointestinal disorders	**209 (49.9)**	**36 (41.9)**	**25 (30.5)**
Nausea	132 (31.5)	19 (22.1)	7 (8.5)
Constipation	57 (13.6)	10 (11.6)	7 (8.5)
Vomiting	55 (13.1)	7 (8.1)	6 (7.3)
Diarrhea	54 (12.9)	12 (14.0)	11 (13.4)
Abdominal pain	17 (4.1)	7 (8.1)	5 (6.1)
Abdominal pain upper	17 (4.1)	3 (3.5)	6 (7.3)
Blood and lymphatic system disorders	**176 (42.0)**	**37 (43.0)**	**30 (36.6)**
Neutropenia	117 (27.9)	23 (26.7)	22 (26.8)
Anemia	48 (11.5)	18 (20.9)	9 (11.0)
Thrombocytopenia	29 (6.9)	2 (2.3)	2 (2.4)
Leukopenia	27 (6.4)	5 (5.8)	4 (4.9)
Febrile neutropenia	21 (5.0)	6 (7.0)	4 (4.9)
Infections and infestations	**174 (41.5)**	**39 (45.3)**	**28 (34.1)**
Nasopharyngitis	27 (6.4)	2 (2.3)	5 (6.1)
Bronchitis	23 (5.5)	2 (2.3)	1 (1.2)
Urinary tract infection	19 (4.5)	3 (3.5)	6 (7.3)
Lower respiratory tract infection	15 (3.6)	7 (8.1)	2 (2.4)
Investigations	**134 (32.0)**	**12 (14.0)**	**16 (19.5)**
Neutrophil count decreased	59 (14.1)	6 (7.0)	8 (9.8)

Platelet count decreased	38 (9.1)	2 (2.3)	4 (4.9)
Lymphocyte count decreased	26 (6.2)	2 (2.3)	0
White blood cell count decreased	23 (5.5)	4 (4.7)	2 (2.4)
Skin and subcutaneous tissue disorders	**134 (32.0)**	**25 (29.1)**	**13 (15.9)**
Rash	48 (11.5)	3 (3.5)	5 (6.1)
Pruritus	30 (7.2)	3 (3.5)	3 (3.7)
Respiratory, thoracic and mediastinal disorders	**123 (29.4)**	**17 (19.8)**	**22 (26.8)**
Cough	53 (12.6)	9 (10.5)	8 (9.8)
Dyspnea	35 (8.4)	3 (3.5)	3 (3.7)
Nervous system disorders	**95 (22.7)**	**22 (25.6)**	**24 (29.3)**
Headache	31 (7.4)	7 (8.1)	6 (7.3)
Paresthesia	9 (2.1)	5 (5.8)	6 (7.3)
Neuropathy peripheral	0	6 (7.0)	11 (13.4)
Musculoskeletal and connective tissue disorders	**83 (19.8)**	**15 (17.4)**	**17 (20.7)**
Back pain	19 (4.5)	4 (4.7)	3 (3.7)
Arthralgia	13 (3.1)	2 (2.3)	5 (6.1)
Metabolism and nutrition disorders	**59 (14.1)**	**8 (9.3)**	**9 (11.0)**
Decreased appetite	21 (5.0)	1 (1.2)	3 (3.7)
Injury, poisoning and procedural complications	**42 (10.0)**	**6 (7.0)**	**7 (8.5)**
Infusion related reaction	12 (2.9)	4 (4.7)	6 (7.3)

Benda: bendamustine; CHOP: cyclophosphamide, doxorubicin, vincristine and prednisone; CVP: cyclophosphamide, vincristine and prednisone; TEAE: treatment-emergent adverse event.

Supplementary Table S5. **Tumor responses before randomization in Maintenance II (ITT_{rand} population).**

n (%)		R-SC n=138	Observation n=138	R-SC n=138	Observation n=138
		End of Induction		End of Maintenance I	
OR[a]		137 (99.3)	137 (99.3)	137 (99.3)	138 (100)
	CR	50 (36.2)	46 (33.3)	76 (55.1)	79 (57.2)
	PR	87 (63.0)	91 (65.9)	61 (44.2)	59 (42.8)
SD		1 (0.7)[b]	1 (0.7)[c]	0	0
PD		0	0	1 (0.7)[d]	0

CR: complete response; OR: overall response; PD: disease progression; PR: partial response; R-SC: rituximab subcutaneous; SD: stable disease.

[a]OR rate = proportion of responders at the end of Induction. A responder was defined as a patient experiencing either CR or PR according to Cheson response criteria[32] or recommendations for Waldenström macroglobulinemia.

[b]Patient with follicular lymphoma treated with bendamustine was in OR at end of Maintenance I but discontinued (own request).

[c]Patient with marginal zone lymphoma treated with bendamustine was in PR at end of Maintenance I, and completed study per protocol.

[d]Patient was randomized to rituximab in Maintenance II before computed tomography scan tumor assessment result was available; this was recorded as a major protocol violation. The patient did not receive treatment in Maintenance II.

Supplementary Table S6. Progression-free survival (PFSreg) and overall survival (OSreg) according to NHL disease subtype.

			Maintenance II	
n	**Induction**	**Maintenance I**	**Rituximab**	**Observation**
FL	**397**	**294**	**73**	**77**
PFS_{reg}, number with event	185	122	12	16
Progression	141	99	10	13
Deaths	44	23	2	3
Median (95% CI), months	54.70 (42.87–71.36)	68.73 (60.02–NR)	NR (NR–NR)	NR (68.73–NR)
OS_{reg}				
Deaths	103	59	6	5
Median (95% CI), months	NR (NR–NR)	NR (NR–NR)	NR (NR–NR)	NR (NR–NR)
WM/LPL	**122**	**85**	**28**	**25**
PFS_{reg}, number with event	49	27	3	4
Progression	32	16	1	2
Deaths	17	11	2	2
Median (95% CI), months	70.60 (43.73–NR)	70.60 (59.33–NR)	NR (NR–NR)	70.60 (NR–NR)
OS_{reg}				
Deaths	27	14	2	2
Median (95% CI), months	NR (NR–NR)	NR (NR–NR)	NR (NR–NR)	NR (NR–NR)

MZL	**148**	**105**	**36**	**35**
PFS_{reg}, number with event	51	27	4	7
Progression	38	23	4	7
Deaths	13	4	–	–
Median (95% CI), months	NR (55.49–NR)	NR (NR–NR)	NR (NR–NR)	NR (55.49–NR)
OS_{reg}				
Deaths	27	10	2	1
Median (95% CI), months	NR (NR–NR)	NR (NR–NR)	NR (NR–NR)	NR (NR–NR)

CI, confidence interval; FL: follicular lymphoma; MZL: marginal zone lymphoma; NHL: non-Hodgkin lymphoma; NR, not reached; WM/LPL: Waldenström macroglobulinemia/lymphoplasmacytic lymphoma.

Supplementary Table S7. Overall response rate at the end of Induction by chemotherapy group and by patients remaining at the start of each subsequent study phase. Data are shown as number of responders/total number of responders + non-responders (%; 95% confidence interval).

Induction chemotherapy	Induction (N=692)[a]	Maintenance I (N=494)	Maintenance II (Rituximab arm; N=138)
Bendamustine	362/419 (86.4; 82.7–89.5)	296/302 (98.0; 95.7–99.3)	79/80 (98.8; 93.2–100)
CHOP	75/86 (87.2; 78.3–93.4)	67/67 (100; 94.6–100)	20/20 (100; 83.2–100)
CVP	69/82 (84.1; 74.4–91.3)	64/66 (97.0; 89.5–99.6)	26/26 (100; 86.8–100)
Other	80/104 (76.9; 67.6–84.6)	59/59 (100; 93.9–100)	12/12 (100; 73.5–100)

CHOP: cyclophosphamide, doxorubicin, vincristine and prednisone; CVP: cyclophosphamide, vincristine and prednisone.

[a]One patient received rituximab but no chemotherapy.