Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Robak T, Huang H, Jin J, et al. Bortezomib-based therapy for newly diagnosed mantle-cell lymphoma. N Engl J Med 2015;372:944-53. DOI: 10.1056/NEJMoa1412096

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SUPPLEMENTARY APPENDIX

Supplement to: Robak T, Huang H, Jin J, et al. Bortezomib-Based Therapy for Newly Diagnosed Mantle Cell Lymphoma.

Contents

LYM-3002 Investigators

Patients were recruited from 128 centers across 28 countries in four continents. The following investigators (listed by country) enrolled patients into the study:

Austria – Johannes Drach, Richard Greil; *Belgium* – Gregor Verhoef, Andre Bosly, Fritz Offner, Ann Van De Velde, Achiel Van Hoof, Steven Van Steenweghen, Pierre Zachee, Bernard De Prijck; *Brazil* – Juliana Pereira, Bernardo Garichochea, Vladimir Lima, Marcelo Capra, Adriana Sheliga, Carmino Souza, Patricia Santi; *Canada* – Andrew Belch, Michael Crump; *Chile* – Carmen Cao; *Colombia* – Kenny Mauricio Galvez Cardenas, Sergio Cancelado; *Czech Republic* – Jiri Mayer, Jan Novak, David Belada; *France* – Remy Gressin, Steven Le Gouill, Mario Ojeda-Uribe; *Germany* – Ernst Späth-Schwalbe, Georg Heß, Maike De Wit; *Hungary* – Judit Demeter, Miklós Egyed, Zita Borbenyi, Zoltán Gasztonyi, Árpád Illes, Miklos Udvardy; *India* – Govind Babu, Ashis Mukhopadhyay, Sreejith Nair; *Israel* – Ofer Shpilberg, Irit Avivi, Dina Ben Yehuda; *Italy* – Massimo Federico, Guiseppe Rossi, Michele Baccarani, Enrica Morra, Umberto Vitolo; *Japan* – Yoshiharu Maeda, Michinori Ogura, Rumiko Okamoto, Masafumi Taniwaki, Yasuhito Terui, Kensei Tobinai, Naokuni Uike, Kiyoshi Ando, Kenichi Ishizawa, Mitsutoshi Kurosawa, Akihiro Tomita, Tomohiro Kinoshita, Toshiki Uchida; *People's Republic of China* –Huiqiang Huang, Jie Jin, Jun Zhu, Ting Liu, Xiaonan Hong, Xiaoyan Ke, Huaqing Wang, Zhixiang Shen, Yuankai Shi, Zhao Wang; *Poland* – Tadeusz Robak, Jan Maciej Zaucha, Sebastian Grosicki; *Portugal* – Adriana Teixeira, Herlander Marques, Margarida Marques; *Republic of Korea* – Sung-Soo Yoon, Cheol Won Suh; *Romania* – Cristina Ileana Burcoveanu, Razvan Stoia, Horia Bumbea, Cristina Ligia Cebotaru, Cristina-Ligia Truica; *Russian Federation* – Olga Samoilova, Julia Alexeeva, Evgenii Osmanov, Irina Lysenko, Alexander Suvorov, Oleg Gladkov, Georgii Manikhas,

Tatiana Scheider, Nuriet Khuageva, Alexy Kuzmin, Kudrat Abdulkadryrov, Irina Bulavina, Yuri Dunaev, Lyudmila Kuzina, Anatoly Golenkov, Marina Golubeva, Olga Serduk, Yurii Lorie, Viacheslav Pavlov, Vladimir Merkulov, Dmitry Udovitsa; *Singapore* – Yeow Tee Goh; *Spain* – Reyes Arranz, Dolores, Caballero Gabarrón, Albert Oriol Rocafiguera, Francisco Javier Capote, Joaquín Díaz, Eva Gonzalez-Barca; *Taiwan* – Lee-Yung Shih; *Thailand* – Noppadol Siritanaratkul, Udomsak Bunworasate, Weerasak Nawarawong, Suporn Chuncharunee; *Tunisia* – Balkis Meddeb, Amel Mezlini; *Turkey* – Bulent Undar, Mahmut Gumus; *Ukraine* – Halyna Pylypenko, Kateryna Vilchevskaya, Zvenyslava Masliak, Grigoriy Rekhtman, Polina Kaplan, Iryna Kryachok, Maryna Kyselyova; *United States of America* – Charles Farber, Vijay Rao Phooshkooru, Ali Khojasteh.

Additional Methodology

Key Inclusion and Exclusion Criteria

Male or female patients aged ≥18 years with a diagnosis of mantle cell lymphoma (MCL) (stage II, III, or IV), as determined by histology and either expression of cyclin D1 (in association with CD20 and CD5) or evidence of t(11;14) translocation (by cytogenetics, fluorescence in-situ hybridization, or polymerase chain reaction), were enrolled. In all patients, a paraffin-embedded biopsy tissue block (preferably of lymph node origin) was sent to one of two central laboratories (Diagnostic Cytology Laboratories, Indianapolis, IN, USA, or PhenoPath Laboratories, Seattle, WA, USA) for confirmation of diagnosis of MCL. Patients also had to be ineligible for stem cell transplantation according to the treating physician (e.g., due to age or comorbid conditions). Prior to a protocol amendment, this criterion was worded such that patients who were considered ineligible for transplantation for other than clinical reasons (e.g., because stem cell transplantation was not available or because the patient refused transplantation) were also considered eligible for the study. Additional inclusion criteria for the study were: at least one site of measurable disease; no prior treatment for MCL; Eastern Cooperative Oncology Group performance status of ≤2; absolute neutrophil count ≥1500 cells per microliter; platelet count ≥100,000 cells per microliter, or ≥75,000 cells per microliter if thrombocytopenia was considered by the investigator to be secondary to MCL (e.g., due to bone marrow infiltration or sequestration from splenomegaly); alanine transaminase level ≤3 times the upper limit of normal; aspartate transaminase level ≤3 times the upper limit of normal; total bilirubin level ≤1.5 times the upper limit of normal; and calculated creatinine clearance ≥20 milliliters per minute. Female patients had to be post-menopausal for ≥1 year, surgically sterile, or practicing an

effective method of birth control (as described in the protocol), and have a negative serum beta-human chorionic gonadotropin or urine pregnancy test at screening; they also had to agree to continue using birth control measures for ≥6 months after terminating treatment. Male patients had to agree to use an acceptable method of contraception for the duration of the study.

Patients were excluded from the study if they had received prior treatment with bortezomib, or any prior antineoplastic (including unconjugated therapeutic antibodies), experimental, or radiation therapy, or radio-immunoconjugates or toxin immunoconjugates to treat MCL. If doxorubicin had been used previously to treat another condition, the maximum prior dose and exposure must not have exceeded 150 mg per square meter. A short course of low-dose prednisone or equivalent steroids (maximum duration, 10 days; dose, ≤100 mg per day) was allowed to treat symptoms in patients with advanced disease prior to randomization. Further exclusion criteria were: major surgery within 2 weeks before randomization; peripheral neuropathy or neuropathic pain of grade ≥2 (by investigator assessment); diagnosis or treatment of a malignancy other than MCL within 1 year of randomization, or previous diagnosis of another malignancy with radiographic or biochemical evidence of residual disease (except completely resected basal cell carcinoma, squamous cell carcinoma of the skin, or an in-situ malignancy); active systemic infection requiring treatment, a known diagnosis of human HIV, or active hepatitis B (hepatitis B carriers were permitted); serious pre-existing medical condition (e.g., cardiac failure [New York Heart Association Class III or IV, or left ventricular ejection fraction <50%], active peptic ulceration, uncontrolled diabetes mellitus, or acute diffuse infiltrative pulmonary disease), or psychiatric illness likely to

interfere with study participation; and concurrent treatment with another investigational agent.

Permitted Concomitant Treatments and Prophylactic Medications

All concomitant medications for medical conditions other than MCL were permitted as clinically indicated. Supportive therapies (e.g., antiemetics/antinauseants, loperamide for diarrhea, MESNA for prevention of hemorrhagic cystitis, allopurinol for patients at risk of tumor lysis syndrome, antiviral prophylaxis for herpes, lamivudine or equivalent prophylaxis for hepatitis B surface antigen-positive patients, and platelet/red blood cell transfusions) were allowed, as required. Antiviral prophylaxis for herpes zoster reactivation was made mandatory in both treatment arms following the third protocol amendment. Lamivudine (100 mg per day orally) or equivalent prophylaxis was recommended until 8 weeks after the last dose of chemotherapy for all hepatitis B surface antigen-positive patients following the fourth protocol amendment.

Colony-stimulating growth factors could be administered at any time during the study for the prevention of neutropenia and for the management of treatment-emergent toxicities. Premedication for rituximab infusion (i.e., acetaminophen, diphenhydramine, and steroids) could be considered before each infusion of rituximab to attenuate infusion reactions. Concomitant antineoplastic agents, other than bortezomib, rituximab, cyclophosphamide, doxorubicin, vincristine, or prednisone, were not allowed; however, medications that may have had an antineoplastic activity but which were to be taken for other reasons (e.g., megestrol, COX-2 inhibitors, and bisphosphonates) were permitted. Patients were not permitted

to undergo radiation therapy, or to receive any experimental agent other than that defined in the protocol.

Pre-Specified Secondary Endpoints

Secondary endpoints of the study included: overall response rate (defined as the proportion of patients achieving a complete response, unconfirmed complete response, or partial response) and complete response rate (defined as the proportion of patients achieving a complete response or unconfirmed complete response); time to response (defined as the duration between randomization and initial documentation of response); duration of radiologic response and duration of complete response (defined as the duration between initial documentation of response or complete response, respectively, and first documented evidence of progressive disease or death due to progressive disease); time to progression; time to next anti-lymphoma therapy and subsequent therapies received; treatment-free interval; overall survival; and safety.

Time-to-Event Analyses

Time to progression was defined as the duration from the date of randomization until the date of first documented evidence of progressive disease or relapse for patients who experienced complete response or unconfirmed complete response. Time to next anti-lymphoma therapy was measured from the date of initiation of study treatment as per protocol to the start date of new anti-lymphoma therapy. Death due to disease progression prior to subsequent therapy was considered as an event. Otherwise, time to next anti-lymphoma treatment was censored at the patients' date of death or the last date known to be alive.

The treatment-free interval was measured from the date of last dose plus 1 day to the start date of the new treatment. Death due to disease progression prior to subsequent therapy was considered as an event. Otherwise, treatment-free interval was censored at the date of death or the last date known to be alive.

Overall survival was measured from the date of randomization to the date of patient death. If the patient was alive or the vital status was unknown, overall survival was censored at the date that the patient was last known to be alive.

Immunohistochemical Analysis of Ki-67 Expression

Immunohistochemical analysis of Ki-67 expression was done according to the consensus guidelines of the pathology panel of the European MCL Network.[1] Ki-67 expression was assessed in paraffin-embedded, formalin-fixed or frozen tumor samples obtained from consenting patients. Paraffin-embedded tissue sections were deparaffinized, rehydrated, and blocked for endogenous peroxidase, prior to being treated with hot citrate buffer (pH 6) under pressure to unmask epitopes. Sections were incubated with monoclonal mouse anti-human Ki-67 antibody (MIB-1 clone, Dako) followed by detection using the Dako Envision Plus™ (mouse) kit, and counterstaining with hematoxylin. All sections were reviewed by a board-certified hematopathologist at the central PhenoPath laboratory (Seattle, WA, USA). Ki-67-positive status was defined as >10% expression on an ordinal scale (the accepted cut-off for prognostic significance).[2] A cut-off of 30% Ki-67 expression on an ordinal scale was additionally used for dichotomizing patients in analysis of progression-free survival (Ki-67 positive: >30%; Ki-67 low/no expression: ≤30%).

Definition of Analysis Populations

The intent-to-treat population, defined as all randomized patients, was used for analyses of all primary and secondary efficacy endpoints, with the exception of overall and complete response rates (which were assessed in the response-evaluable population) and treatment-free interval (which was assessed in the safety population). The response-evaluable population included all patients in the intent-to-treat population who had received ≥1 dose of study medication, had ≥1 measurable tumor mass (>1.5 centimeters in the longest dimension and >1.0 centimeter in the short axis) at baseline, and had ≥1 post-baseline tumor assessment by independent review committee, prior to subsequent anti-lymphoma treatment. The safety population included all randomized patients who received at least one dose of study medication.

Supplementary Figures

Figure S1. Patient Disposition (CONSORT Diagram).

R-CHOP denotes rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, VR-CAP bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone.

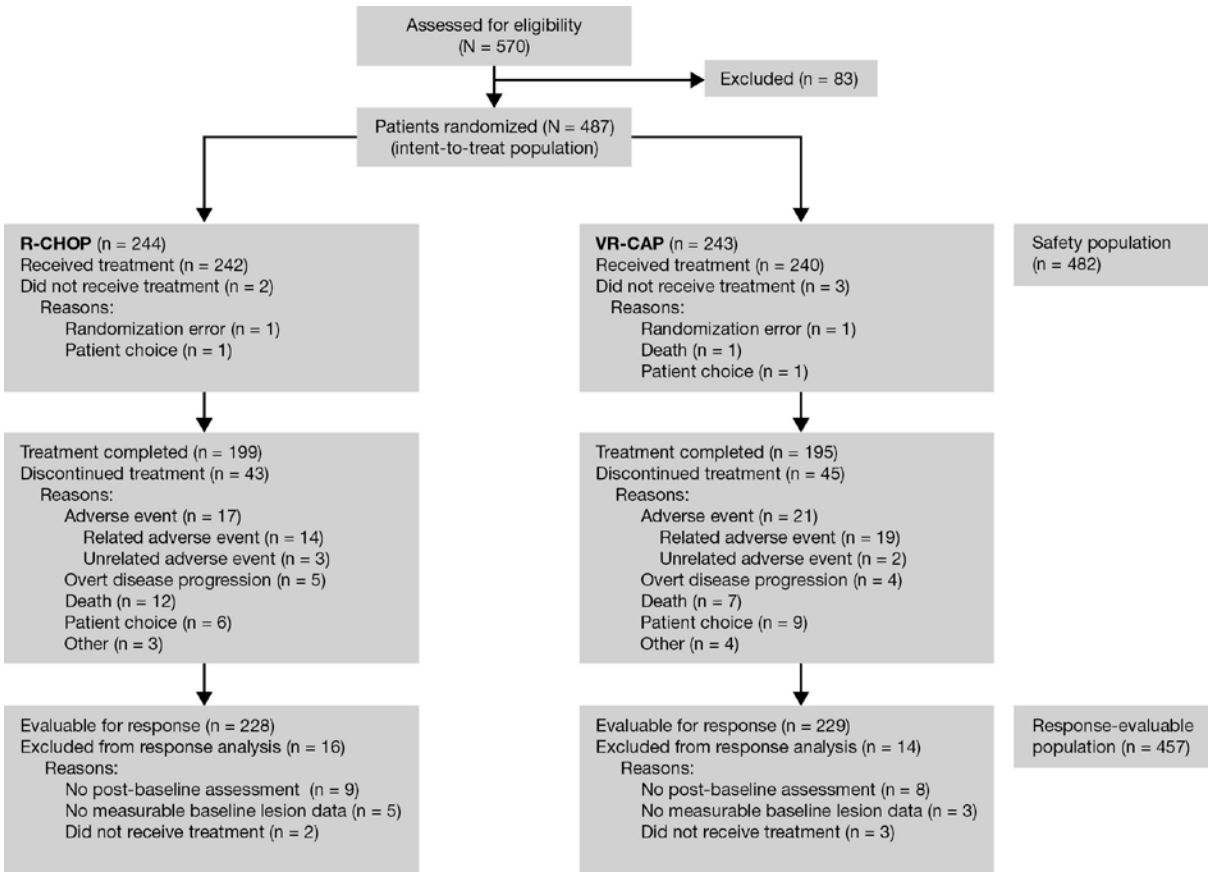
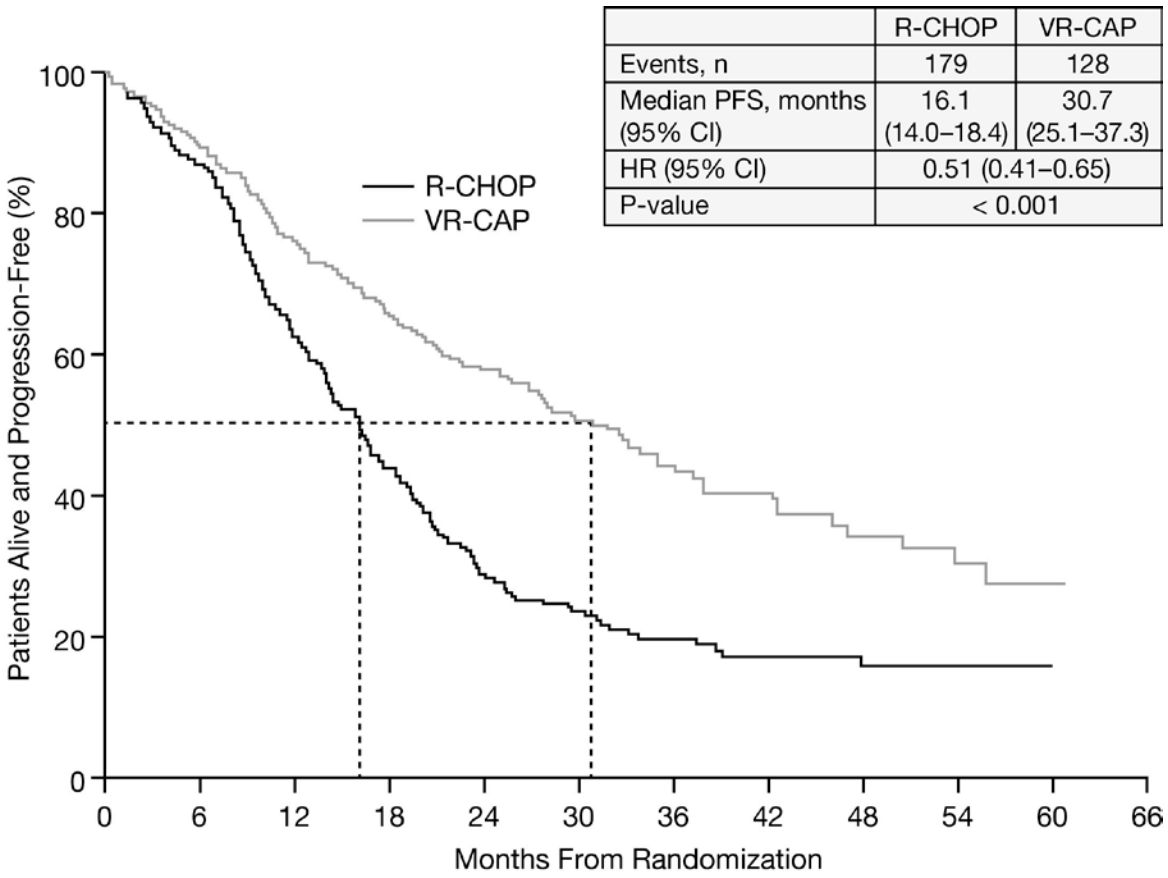


Figure S2. Kaplan-Meier Analysis of Progression-Free Survival by Investigator Assessment (Intent-to-Treat Population).

CI denotes confidence interval, HR hazard ratio, PFS progression-free survival, R-CHOP rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, VR-CAP bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone.



	R-CHOP	VR-CAP
Events, n	179	128
Median PFS, months (95% CI)	16.1 (14.0–18.4)	30.7 (25.1–37.3)
HR (95% CI)	0.51 (0.41–0.65)	
P-value	< 0.001	

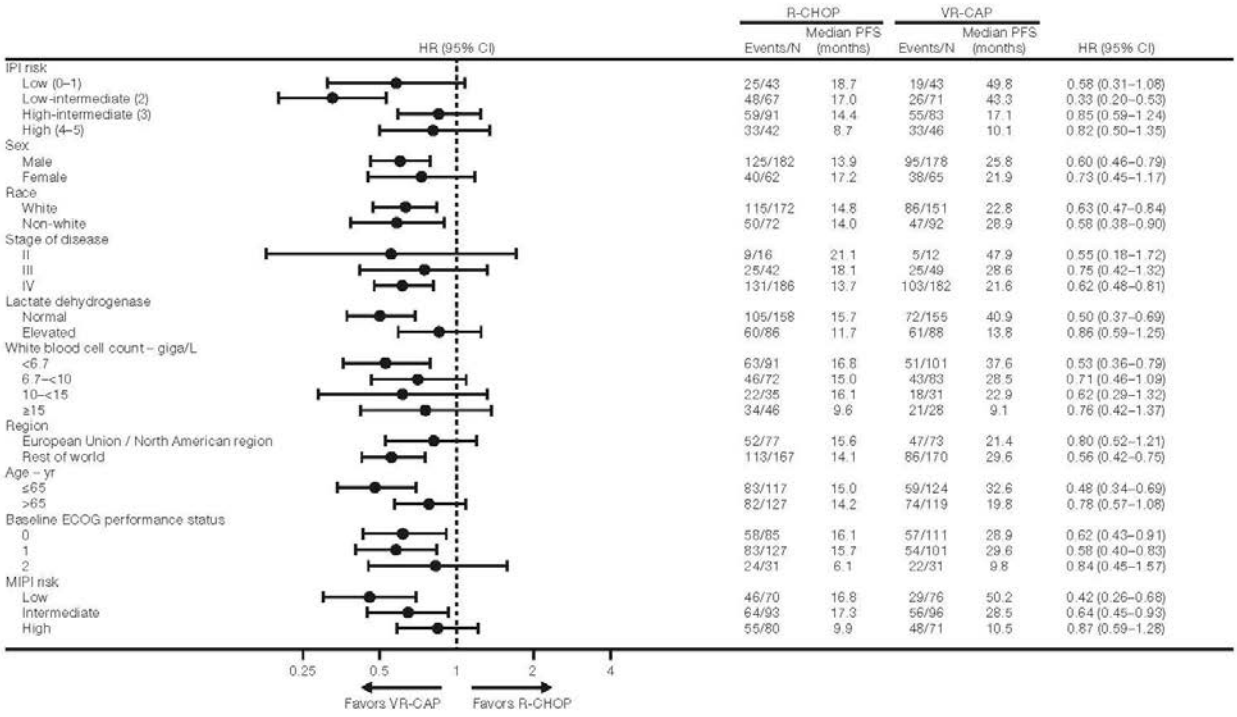
Number of patients at risk:

R-CHOP	244	194	137	96	61	42	25	18	11	4	1	0
VR-CAP	243	200	166	140	117	85	52	36	22	13	2	0

Figure S3. Pre-Specified Subgroup Analyses of Progression-Free Survival by Baseline Characteristics per Independent Review Committee Assessment (Intent-to-Treat Population).

CI denotes confidence interval, ECOG Eastern Cooperative Oncology Group, HR hazard ratio, IPI International Prognostic Index, MIPI, Mantle Cell Lymphoma-specific International Prognostic Index, PFS progression-free survival, R-CHOP rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, VR-CAP bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone.

In the pre-planned analysis, data for the European Union and North American region were analyzed separately (HRs of 0.68 and 4.31, respectively). As the North American subgroup comprised only 14 patients, the European Union and North American regions were combined in this analysis.



Supplementary Tables

Table S1. International Prognostic Index (IPI) for Mantle Cell Lymphoma Calculated by Sum of the Five Risk Factors*

Risk Factors	Score
Age > 60 years	1
Mantle cell lymphoma stage III or IV at diagnosis	1
ECOG performance status >1	1
More than one extranodal site involvement	1
LDH above normal limits	1

* ECOG denotes Eastern Cooperative Oncology Group, LDH, lactate dehydrogenase

Table S2. Modified International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphoma (IWRC) Criteria (per Cheson et al., 2007[3])

Response Assessment	Modified IWRC Criteria
Complete Response (CR)	Requires ALL of the following: 1. Complete disappearance of all detectable clinical and radiological evidence of disease and disease-related symptoms, and normalization of biochemical abnormalities definitely assignable to lymphoma (e.g., lactate dehydrogenase [LDH]) if present before therapy. 2. All measurable lymph nodes and nodal masses must have regressed on computed tomography [CT] to normal size (≤1.5 cm in their greatest transverse diameter for nodes >1.5 cm before therapy). 3. Non-measurable and assessable nodes that were 1.1 to 1.5 cm in their greatest transverse diameter before treatment must have decreased to ≤1 cm in their greatest transverse diameter after treatment, or by more than 75% in the sum of the products of the greatest diameters (SPD), as visually estimated. 4. The spleen or liver, if considered enlarged due to involvement with lymphoma before therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies. Similarly, other organs considered to be enlarged before therapy due to involvement by lymphoma such as kidneys, must have decreased in size. 5. If the bone marrow was involved by lymphoma, indeterminate or not adequately assessed during screening, an adequate aspirate and biopsy of the same site must be clear of lymphoma. 6. All extranodal sites of disease must have completely

	disappeared.
Unconfirmed Complete Response (CRu)	Requires: That the first and fourth criteria for CR be satisfied, however: 1. Any residual lymph node mass >1.5 cm in longest transverse dimension or extranodal site of disease (irrespective of size) must have regressed by more than 75% of the product of the longest perpendicular dimensions compared to the pretreatment baseline. 2. The bone marrow aspirate may be indeterminate (contain increased number or size of lymphoid aggregates without cytologic or architectural atypia). 3. If there are residual masses in a patient who would otherwise be considered to have achieved a CR or CRu, the patient should be classified as a partial responder.
Partial Response (PR)	Requires ALL of the following: 1. At least a 50% decrease in the SPD of the measurable sites of disease. 2. No increase should be observed in any site of disease that meet the criteria for relapsed or progressive disease. 3. Non-measurable nodes and nodules must regress by ≥50% in their SPD or, for single non-measurable lesions, in the greatest transverse diameter, as visually estimated. 4. Bone marrow assessment is irrelevant for determination of a PR if the sample was positive before treatment. However, patients who achieve a CR by the above criteria, but who have persistent morphologic bone marrow involvement will be considered partial responders. When the bone marrow was involved before therapy and a clinical CR was achieved, but with no bone marrow assessment after treatment, patients should be considered partial responders. 5. No new sites of disease should be observed that meet the criteria for relapsed or progressive disease.
Stable Disease	Defined as the following:

(SD)	A patient is considered to have SD when he or she fails to attain the criteria needed for a CR or PR, but does not fulfill those for progressive disease (see below).
Progressive Disease (Includes Relapsed Disease)	Requires any one of the following: 1. A) ≥50% increase from nadir in the SPD of all measurable sites of disease at the time that progressive or relapsed disease is identified and the absolute change in at least 1 dimension is ≥0.5 cm for at least 1 lesion; or B) ≥50% increase in the long axis of any measurable site of disease at the time that progressive or relapsed disease is identified and the absolute change in the long axis is ≥0.5 cm. 2. A) ≥50% increase from nadir in the SPD of all non-measurable sites of disease (excluding truly assessable disease), as visually estimated, and the absolute change in at least 1 dimension is ≥0.5 cm for at least 1 non-measured lesion as estimated visually; or B) ≥50% increase in the long axis of any non-measurable site of disease (excluding truly assessable disease), and the absolute change in the long axis is ≥0.5 cm, as estimated visually. 3. ≥50% increase from nadir in any truly assessable site of disease, as visually estimated. 4. Appearance of any new lymph node site of disease that measures >1.5 cm in long axis and >1.0 cm in short axis, any new unequivocal extranodal site of disease (irrespective of size), or unequivocal evidence of a new site of assessable disease (for example effusions, ascites, masses with indistinct borders, new involvement of the bone marrow). 5. Appearance of a new organ enlargement or unequivocal increase of an organ enlargement that was present since baseline.

Table S3. Patient Demographics and Baseline Characteristics (Intent-To-Treat Population).†

Variable	R-CHOP (n = 244)	VR-CAP (n = 243)	Total (N = 487)
Age			
Median — yr	66	65	66
Range — yr	34–82	26–88	26–88
Subgroup — no. (%)			
≥60 yr	177 (73)	178 (73)	355 (73)
Male — no. (%)	182 (75)	178 (73)	360 (74)
Race — no. (%)*			
White	172 (71)	151 (62)	323 (66)
Asian	68 (28)	88 (36)	156 (32)
Black or African American	0	3 (1)	3 (<1)
Other	4 (2)	1 (<1)	5 (1)
ECOG performance status — no. (%)*‡			
0	85 (35)	111 (46)	196 (40)
1	127 (52)	101 (42)	228 (47)
2	31 (13)	31 (13)	62 (13)
Missing	1 (<1)	0	1 (<1)
IPI score (risk category) — no. (%)‡§			
0–1 (low)	38 (16)	38 (16)	76 (16)
2 (low–intermediate)	71 (29)	75 (31)	146 (30)
3 (high–intermediate)	88 (36)	84 (35)	172 (35)
4–5 (high)	47 (19)	46 (19)	93 (19)

Variable	R-CHOP (n = 244)	VR-CAP (n = 243)	Total (N = 487)
MIPI risk category — no. (%)‡			
Low	70 (29)	76 (31)	146 (30)
Intermediate	93 (38)	96 (40)	189 (39)
High	80 (33)	71 (29)	151 (31)
Missing	1 (<1)	0	1 (<1)
Disease stage at diagnosis — no. (%)‡			
II	16 (7)	12 (5)	28 (6)
III	42 (17)	49 (20)	91 (19)
IV	186 (76)	182 (75)	368 (76)
Elevated LDH — no. (%)	86 (35)	88 (36)	174 (36)
Bone marrow involvement — no. (%)	171 (70)	165 (68)	336 (69)
Extranodal involvement — no. (%)§§	137 (56)	139 (57)	276 (57)
Histological subtype — no. (%)			
Blastoid	28 (12)	25 (11)	53 (11)
Nodular	97 (41)	109 (46)	206 (43)
Reason for transplant ineligibility — no. (%)§§¶			
Age ≥60 yr and/or medically ineligible for transplantation	202 (83)	205 (84)	407 (84)
Age <60 yr and not considered for transplantation¶¶	42 (17)	38 (16)	80 (16)
Hematology laboratory parameters — mean			
Platelets — x 10^9/L	217.7	190.7	204.2

Variable	R-CHOP (n = 244)	VR-CAP (n = 243)	Total (N = 487)
WBC — x 10^9/L	12.74	10.85	11.80
Neutrophils — x 10^9/L	4.77	4.49	4.63
Lymphocytes — x 10^9/L	5.51	5.16	5.34
Hemoglobin — g/L	120.8	123.4	123.0

* P ≤ 0.05.

† ECOG denotes Eastern Cooperative Oncology Group, IPI International Prognostic Index, LDH lactate dehydrogenase, MIPI Mantle Cell Lymphoma-specific International Prognostic Index, R-CHOP rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, VR-CAP bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone, WBC white blood cells.

‡ Sum of percentages may not equal 100% due to rounding.

§ Data from stratification.

§§ Based on the sponsor's medical monitor assessment.

¶ Most patients were enrolled based on ineligibility for transplantation due to medical reasons (age ≥60 years or the presence of coexisting medical conditions, in accordance with current protocols).[4]

¶¶ Not considered for transplantation due to socio-economic reasons (financial affordability), decision not to undergo the procedure, or lack of transplant availability.

Table S4. Baseline Ki-67 Expression Status and MIPIb Risk Category in the Subset of Patients Undergoing Ki-67 Assessment.*

Ki-67 Evaluable Patients	**R-CHOP (n = 164)**	**VR-CAP (n = 163)**
Ki-67 status — no. (%)†		
Positive (Ki-67 >10%)	82 (50)	84 (52)
Low/no expression (Ki-67 ≤10%)	82 (50)	79 (48)
MIPIb risk category — no. (%)		
Low risk	23 (14)	23 (14)
Intermediate risk	72 (44)	74 (45)
High risk	69 (42)	66 (40)

* MIPIb denotes Mantle Cell Lymphoma-specific International Prognostic Index with biologic component, R-CHOP rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, VR-CAP bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone.

† Ki-67 staining performed by central pathology laboratory.

Table S5. Treatment Exposure.*

Variable	R-CHOP (n = 244)	VR-CAP (n = 243)
Treatment cycles received — no.		
Median	6	6
Range	1–8	1–8
Received ≥6 cycles — no. (%)	203 (83)	203 (84)
Received 8 cycles — no. (%)	42 (17)	32 (13)
Treatment duration — weeks		
Median	16.1	17.6
Range	0.4–32.7	0.7–30.6
Completed treatment — no. (%)†	199 (82)	195 (80)
Discontinued treatment — no. (%)†	43 (18)	45 (19)
Relative dose intensity‡	n = 242	n = 240
— Mean (standard deviation) — %		
Rituximab	100 (2)	100 (1)
Cyclophosphamide	98 (6)	93 (10)
Doxorubicin	99 (5)	97 (9)
Prednisone	96 (12)	95 (12)
Vincristine§ / Bortezomib	80 (11)	82 (15)

* R-CHOP denotes rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, VR-CAP bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone.

† Sum of percentages may not equal 100% because five patients who did not receive study treatment were not counted.

‡ Dose received versus dose prescribed with the optimal being 100%.

§ Vincristine total dose was capped at a maximum of 2 mg.

Table S6. Summary of Primary and Sensitivity Analyses of Progression-Free Survival.†

		Median (months)		
	Events (n)	**R-CHOP**	**VR-CAP**	**Hazard Ratio (95% CI)**
Progression-free survival by IRC (ITT)				
Primary analysis	298	14.4	24.7	0.63 (0.50–0.79)*
Unstratified analysis	298	14.4	24.7	0.62 (0.50–0.79)*
No censoring for subsequent antineoplastic therapy	302	14.4	24.0	0.63 (0.50–0.80)*
Censoring for PD after >1 missing adequate tumor assessment	291	14.4	25.8	0.62 (0.49–0.78)*
Using IRC alternative assessments of transient fluid collection/transient lesions as basis for PD	288	14.8	28.5	0.56 (0.44–0.71)*
Progression-free survival by IRC (PP)	282	14.8	27.9	0.59 (0.46–0.75)*
Progression-free survival by IRC	287	14.8	24.0	0.64 (0.50–0.81)*

		Median (months)		
	Events (n)	**R-CHOP**	**VR-CAP**	**Hazard Ratio (95% CI)**
(confirmation of MCL diagnosis) Progression-free survival by investigator (ITT)	307	16.1	30.7	0.51 (0.41–0.65)*

* P ≤ 0.001.

† CI denotes confidence interval, IRC Independent Radiology Review Committee, ITT intent-to-treat population, MCL mantle cell lymphoma, PD progressive disease, PP per-protocol population, R-CHOP rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, VR-CAP bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone.

Table S7. Post-Hoc Analyses of Progression-Free Survival by Ki-67 Expression Status and MIPIb risk Category in the Subset of Patients Undergoing Ki-67 Assessment, and by MIPI Risk Category in the Intent-To-Treat Population.†

	Median Progression-Free Survival (months)		
	R-CHOP	**VR-CAP**	**Hazard Ratio (95% CI)**
Ki-67-positive patients (Ki-67 >10%)‡	n = 82	n = 84	
By IRC	10.9	19.8	0.59 (0.39–0.88)**
By investigator	15.0	29.6	0.42 (0.28–0.64)***
Patients with low/no Ki-67 expression (Ki-67 ≤10%)‡	n = 82	n = 79	
By IRC	17.9	40.9	0.60 (0.38–0.94)*
By investigator	17.6	37.9	0.53 (0.34–0.81)**
Ki-67-positive patients (Ki-67 >30%)‡	n = 15	n = 19	
By IRC	8.6	15.0	0.46 (0.16–1.33)
By investigator	16.8	24.7	0.51 (0.18–1.42)

	Median Progression-Free Survival (months)		
	R-CHOP	**VR-CAP**	**Hazard Ratio (95% CI)**
Patients with low/no Ki-67 expression (Ki-67 ≤30%)‡	n = 149	n = 144	
By IRC	15.7	30.9	0.59 (0.43–0.81)***
By investigator	16.4	33.9	0.47 (0.35–0.65)***
Low-risk MIPIb	n = 23	n = 23	
By IRC	16.6	NE	0.27 (0.10–0.71)**
By investigator	17.6	NE	0.33 (0.13–0.82)*
Intermediate-risk MIPIb	n = 72	n = 74	
By IRC	17.3	40.9	0.50 (0.32–0.79)**
By investigator	17.4	37.3	0.43 (0.27–0.66)***
High-risk MIPIb	n = 69	n = 66	
By IRC	11.9	13.4	0.86 (0.57–1.31)
By investigator	11.9	20.4	0.64 (0.42–0.98)*

	Median Progression-Free Survival (months)		
	R-CHOP	**VR-CAP**	**Hazard Ratio (95% CI)**
Low-risk MIPI§	n = 70	n = 76	
By IRC	16.8	50.2	0.42 (0.26–0.68)***
By investigator	17.6	46.1	0.46 (0.29–0.73)***
Intermediate-risk MIPI§	n = 93	n = 96	
By IRC	17.3	28.5	0.64 (0.45–0.93)*
By investigator	18.4	36.2	0.44 (0.30–0.64)***
High-risk MIPI§	n = 80	n = 71	
By IRC	9.9	10.5	0.87 (0.59–1.28)
By investigator	9.7	15.0	0.70 (0.47–1.02)

* P ≤ 0.05, **P ≤ 0.01, ***P ≤ 0.001.

† CI denotes confidence interval, IRC Independent Radiology Review Committee, MIPI Mantle Cell Lymphoma-specific International Prognostic Index, MIPIb Mantle Cell Lymphoma-specific International Prognostic Index with biologic component, NE

not estimable, R-CHOP rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, VR-CAP bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone.

‡ Ki-67 staining performed by central pathology laboratory.

§ MIPI risk category not available for 1 patient in the R-CHOP arm.

Table S8. Investigator Assessment of Response.†

Endpoint	R-CHOP	VR-CAP	Risk Ratio/Hazard Ratio (95% CI)¶
Best response rate	n = 228	n = 229	
Overall response — no. (%)‡	209 (92)	219 (96)	1.04 (0.99–1.10)
Complete response — no. (%)§	63 (28)	95 (41)	1.49 (1.15–1.92)*
Time to response	n = 228	n = 229	
Median — months	1.6	1.4	1.44 (1.18–1.75)**
Duration of response			
Duration of overall response	n = 209	n = 219	
Median — months (95% CI)	16.1 (13.5–18.4)	34.8 (29.3–44.9)	NA
In complete responders	n = 63	n = 95	
Median — months (95% CI)	22.5 (19.8–30.0)	NE (41.2–NE)	NA
Duration of complete response§	n = 63	n = 95	
Median — months (95% CI)	18.7 (15.6–27.4)	49.8 (37.8–NE)	NA

* P = 0.002, ** P < 0.001.

† CI denotes confidence interval, NA not applicable, NE not estimable, R-CHOP rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, VR-CAP bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone.

‡ Complete response plus unconfirmed complete response plus partial response.

§ Complete response plus unconfirmed complete response.

¶ Hazard ratio for time to response.

Table S9. Most Common (≥5% Incidence in Either Arm) Subsequent Anti-Lymphoma Therapies (Intent-to-Treat Population).*

	R-CHOP (n = 244)	VR-CAP (n = 243)
Patients with subsequent therapy — no. (%)†	132 (54)	82 (34)
Combination regimens — no. (%)	108 (82)	57 (70)
Combination chemotherapy	46 (35)	31 (38)
CHOP	10 (8)	3 (4)
Other	25 (19)	21 (26)
Rituximab + single agent‡ ± steroids or rituximab + steroids	43 (33)	15 (18)
Rituximab + bendamustine	20 (15)	5 (6)
Rituximab + chemotherapy	8 (6)	7 (9)
Rituximab + bortezomib	9 (7)	1 (1)
Other	8 (6)	2 (2)

	R-CHOP (n = 244)	VR-CAP (n = 243)
Rituximab + combination chemotherapy	35 (27)	19 (23)
Rituximab + CHOP	5 (4)	5 (6)
Rituximab + other	21 (16)	6 (7)
Single agent§ + chemotherapy ± steroids or single agent§ + combination chemotherapy ± steroids or single agent§ + steroids	13 (10)	3 (4)
Single agents — no. (%)	53 (40)	37 (45)
Rituximab	16 (12)	6 (7)
Ibrutinib	8 (6)	9 (11)
Chemotherapy	9 (7)	6 (7)
Lenalidomide	9 (7)	6 (7)
Temsirolimus	8 (6)	4 (5)
Bendamustine	3 (2)	7 (9)
Other — no. (%)	13 (10)	6 (7)

	R-CHOP (n = 244)	VR-CAP (n = 243)
Radiotherapy	9 (7)	5 (6)

* R-CHOP rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, VR-CAP bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone.

† Patients may have received several different combination regimens or single agents due to multiple lines of subsequent therapies.

‡ Single agents included bendamustine, lenalidomide, thalidomide, bortezomib, or single-agent chemotherapy.

§ Single agents included bendamustine, lenalidomide, thalidomide, or bortezomib.

Table S10. Overall Safety Profile (Safety Population).*

Adverse Events — no. (%)	R-CHOP (n = 242)	VR-CAP (n = 240)
All-grade adverse events	238 (98)	238 (99)
Drug-related all-grade adverse events	226 (93)	231 (96)
Grade ≥3 adverse events	206 (85)	223 (93)
Drug-related grade ≥3 adverse events	194 (80)	219 (91)
Serious adverse events	72 (30)	90 (38)
Drug-related serious adverse events	50 (21)	78 (32)
Adverse events leading to dose reductions of:		
Rituximab	1 (<1)	0
Cyclophosphamide	26 (11)	75 (31)
Doxorubicin	17 (7)	41 (17)
Prednisone	19 (8)	22 (9)
Vincristine	11 (5)	NA
Bortezomib	NA	97 (40)
Adverse events leading to dose withholding of:		
Rituximab	1 (<1)	2 (1)
Cyclophosphamide	1 (<1)	9 (4)
Doxorubicin	0	8 (3)
Prednisone	3 (1)	6 (3)
Vincristine	20 (8)	NA
Bortezomib	NA	180 (75)†
Adverse events leading to discontinuation	17 (7)	21 (9)

Adverse Events — no. (%)	R-CHOP (n = 242)	VR-CAP (n = 240)
Drug-related adverse events leading to discontinuation	14 (6)	19 (8)
On-treatment deaths (within 30 days of last dose)	14 (6)	11 (5)
Deaths due to adverse events	12 (5)	8 (3)
Deaths due to drug-related adverse events‡	7 (3)	5 (2)

* R-CHOP denotes rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, VR-CAP bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone. NA denotes not applicable.

† The majority of bortezomib dose withholding occurred in cycle 6, in which 94 of 203 (46%) patients treated with bortezomib had a dose withheld. Within individual treatment cycles, bortezomib dose withholding was more frequent on days 8 and 11 relative to days 1 and 4.

‡ Deaths in the R-CHOP arm were due to: tumor lysis syndrome; pneumonia; bronchopneumonia and acute respiratory failure; sepsis; cardiac failure acute; atrial fibrillation and left ventricular failure; diarrhea, hypotension, renal failure, respiratory distress, and convulsion (each n=1). Deaths in the VR-CAP arm were due to: cardiac failure, febrile neutropenia, pneumonia, and sepsis (n=1); pulmonary embolism (n=1); pneumonia (n=2); aspiration and left ventricular dysfunction (n=1).

Table S11. Adverse Events of Clinical Interest: Thrombocytopenia, Neutropenia, and Peripheral Neuropathy (Safety Population).*

Adverse Event	R-CHOP (n = 242)	VR-CAP (n = 240)
Thrombocytopenia — no. (%)		
Any-grade thrombocytopenia	46 (19)	173 (72)
Grade ≥3 thrombocytopenia	14 (6)	136 (57)
Any-grade bleeding adverse events	12 (5)	15 (6)
Grade ≥3 bleeding adverse events	3 (1)	4 (2)
Platelet transfusions†	7 (3)	54 (23)
In patients with platelets <10 x 10^9/L	1 of 1 (100)	10 of 13 (77)
In patients with platelets 10–<25 x 10^9/L	3 of 6 (50)	37 of 70 (53)
Occurring during days 10–14 of treatment cycles	6 of 7 (86)	48 of 54 (89)
Platelet count at platelet transfusion — x 10^9/L		
Mean	54.6	28.3
SD	57.1	22.5
Median	34	21
Range	5–305	2–148
Cycle delays due to thrombocytopenia	5 (2)	11 (5)
Neutropenia — no. (%)		
Any-grade neutropenia	178 (74)	211 (88)
Grade ≥3 neutropenia	162 (67)	203 (85)
Any-grade infection adverse events	112 (46)	143 (60)
Grade ≥3 infection adverse events	33 (14)	51 (21)
Systemic antibacterial use†	156 (65)	194 (81)

Adverse Event	R-CHOP (n = 242)	VR-CAP (n = 240)
Colony-stimulating factor use†	148 (61)	186 (78)
Peripheral neuropathy‡		
Any-grade peripheral neuropathy — no. (%)	69 (29)	73 (30)
Grade ≥3 peripheral neuropathy — no. (%)	10 (4)	18 (8)
Treatment discontinuations due to peripheral neuropathy — no. (%)	1 (<1)	4 (2)
Time to onset of peripheral neuropathy — months		
Median	1.7	2.7
Range	0.1–5.2	0.3–8.4
Peripheral neuropathy events improved/resolved — no. (%)	61 (79)	89 (90)
Peripheral neuropathy events resolved — no. (%)	58 (75)	80 (81)
Time to improvement/resolution of peripheral neuropathy — months		
Median	4.8	1.5
95% CI	2.8–6.4	0.9–2.0
Time to resolution of peripheral neuropathy — months		
Median	5.5	3.0
95% CI	3.9–8.1	1.6–4.7

* CI denotes confidence interval, R-CHOP rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, SD standard deviation, VR-CAP bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone.

† Supportive therapies were permitted per protocol.

‡ Peripheral neuropathy not elsewhere classified, high-level term including peripheral sensory neuropathy, neuropathy peripheral, peripheral motor neuropathy, and peripheral sensorimotor neuropathy.

Supplementary References

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