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ORIGINAL REPORT

Single-Agent Lenalidomide in Patients With Mantle-Cell Lymphoma Who Relapsed or Progressed After or Were Refractory to Bortezomib: Phase II MCL-001 (EMERGE) Study

Andre Goy, Rajni Sinha, Michael E. Williams, Sevgi Kalayoglu Besisik, Johannes Drach, Radhakrishnan Ramchandren, Lei Zhang, Sherri Cicero, Tommy Fu, and Thomas E. Witzig

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Andre Goy, John Theurer Cancer Center at Hackensack University Medical Center, Hackensack; Lei Zhang, Sherri Cicero, and Tommy Fu, Celgene, Summit, NJ; Rajni Sinha, Emory University Winship Cancer Institute, Atlanta, GA; Michael E. Williams, University of Virginia Health System, Charlottesville, VA; Sevgi Kalayoglu Besisik, Istanbul University Faculty of Medicine, Istanbul, Turkey; Johannes Drach, Medical University of Vienna, Vienna, Austria; Radhakrishnan Ramchandren, Karmanos Cancer Institute, Detroit, MI; and Thomas E. Witzig, Mayo Clinic, Rochester, MN.

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Corresponding author: Andre Goy, MD, John Theurer Cancer Center at Hackensack University Medical Center, 20 Prospect Ave, Hackensack, NJ 07601; e-mail: agoy@humed.com.

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ABSTRACT

Purpose
Although dose-intensive strategies or high-dose therapy induction followed by autologous stem-cell transplantation have improved the outcome for patients with mantle-cell lymphoma (MCL), most eventually relapse and subsequently respond poorly to additional therapy. Bortezomib (in the United States) and temsirolimus (in Europe) are currently the only two treatments approved for relapsed disease. Lenalidomide is an immunomodulatory agent with proven tumoricidal and antiproliferative activity in MCL. The MCL-001 (EMERGE) trial is a global, multicenter phase II study examining the safety and efficacy of lenalidomide in patients who had relapsed or were refractory to bortezomib.

Patients and Methods
Lenalidomide 25 mg orally was administered on days 1 through 21 every 28 days until disease progression or intolerance. Primary end points were overall response rate (ORR) and duration of response (DOR); secondary end points included complete response (CR) rate, progression-free survival (PFS), overall survival (OS), and safety.

Results
In all, 134 patients were enrolled with a median age of 67 years and a median of four prior therapies (range, two to 10 prior therapies). The ORR was 28% (7.5% CR/CR unconfirmed) with rapid time to response (median, 2.2 months) and a median DOR of 16.6 months (95% CI, 7.7 to 26.7 months). Median PFS was 4.0 months (95% CI, 3.6 to 5.6 months), and median OS was 19.0 months (95% CI, 12.5 to 23.9 months). The most common grade 3 to 4 adverse events were neutropenia (43%), thrombocytopenia (28%), anemia (11%), pneumonia (8%), and fatigue (7%).

Conclusion
The MCL-001 study demonstrated durable efficacy of lenalidomide with a predictable safety profile in heavily pretreated patients with MCL who had all relapsed or progressed after or were refractory to bortezomib.

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INTRODUCTION

Mantle cell lymphoma (MCL) is an uncommon subtype of non-Hodgkin lymphoma (NHL),[1] accounting for 3% to 6% of NHL.[2-4] Median age at diagnosis is mid to late 60s and patients typically present with advanced-stage disease.[2,5-7] Although overall survival (OS) has improved over the last two decades, MCL remains challenging, especially in the relapsed/refractory setting in which median OS is approximately 1 to 2 years with current therapies.[8-10]

Combination chemotherapy and immunotherapy is the foundation of first-line MCL treatment and, when feasible, dose-intensive/induction strategies followed by high-dose therapy and autologous stem-cell transplantation (HDT-ASCT) consolidation have improved outcomes.[8,11-15] Alternative options in older patients or those with comorbidities include less intensive strategies (eg, bendamustine plus rituximab), some of which may incorporate maintenance strategies to improve duration of disease control.[9,16-18] Following relapse, there are limited options, with minimal benefit from

standard chemotherapy or HDT-ASCT, because patients often become chemotherapy resistant.[13,19,20] Two therapeutic agents are currently approved in the relapsed/refractory setting: bortezomib (a proteasome inhibitor; United States) and temsirolimus (a mammalian target of rapamycin complex 1 inhibitor; Europe).[21,22] Both are limited by intravenous administration and short duration of response (DOR),[23-27] substantiating the need for novel alternatives for these patients.

Lenalidomide (Revlimid; Celgene, Summit, NJ) is an immunomodulatory agent initially studied in multiple myeloma and myelodysplastic syndromes.[28-31] Preclinical studies showed antitumor and antiproliferative activities in leukemia and lymphoma, including MCL.[32-34] Two phase II studies (NHL-002 and NHL-003) reported clinical activity of lenalidomide in heavily pretreated patients with relapsed/refractory aggressive NHL,[35,36] including MCL.[37,38] With a similar dosing schema (25 mg per day orally for 21 of 28 days), responses were consistent between studies, including 35% overall response rate (ORR) for both (12% to 13% complete response [CR]), median DOR of 6.2 months (NHL-002) and 10.6 months (NHL-003), and median progression-free survival (PFS) of 4.0 months (NHL-002) and 3.7 months (NHL-003) across all histologies.[35,36] Interestingly, higher and more durable responses were seen in MCL versus other NHL subtypes. Patients with MCL in NHL-002 showed 53% ORR (20% CR), median DOR of 13.7 months, and median PFS of 5.6 months.[36] Central review in the NHL-003 study showed 35% ORR (12% CR/ CR unconfirmed [CRu]), median DOR of 16.3 months, and median PFS of 8.8 months.[38] Responses were independent of baseline characteristics or prior therapies; most common grade 3 to 4 adverse events (AEs) for patients with MCL in NHL-002 and NHL-003 were neutropenia (40% and 46%) and thrombocytopenia (33% and 30%), respectively.[37,38] On the basis of these encouraging results and limited treatment options in relapsed/refractory MCL, the MCL-001 (EMERGE) phase II study was designed to examine the safety and efficacy of single-agent lenalidomide in heavily pretreated patients who had relapsed, progressed, or were refractory to bortezomib.

PATIENTS AND METHODS

Patients

The institutional review board or independent ethics committee at each participating institution reviewed and approved the study protocol, amendments, and patient's written informed consent before study initiation. Study design and conduct were in accordance with ethical principles of Good Clinical Practice according to International Conference on Harmonization Harmonized Tripartite Guidelines and the Declaration of Helsinki.

Key inclusion criteria were confirmed MCL diagnosis with cyclin-D1 overexpression by immunohistochemistry or t(11;14)(q13;q32) translocation by fluorescent in situ hybridization, age ≥18 years, Eastern Cooperative Oncology Group (ECOG) performance score 0 to 2, absolute neutrophil count ≥ 1,500/μL, platelets ≥ 60,000/μL, and adequate organ function. Diagnosis criteria included measurable lesion (≥ 2 cm by computed tomography [CT]). Patients were required to have prior anthracycline or mitoxantrone, cyclophosphamide, or rituximab therapy and documented relapsed, refractory, or progressive disease (PD) following bortezomib (alone or in combination). The definition of relapse was within 1 year of the last dose of bortezomib and following an initial CR to a bortezomib-containing regimen. Refractory to bortezomib was defined as PD without achieving at least a partial response (PR) during treatment after at least two cycles of a bortezomib-containing regimen. PD was within 1 year of the last dose of bortezomib after achieving a PR to a bortezomib-containing regimen. Patients who relapsed after HDT-ASCT were eligible, and there was no limitation for the number of prior therapies.

Key exclusion criteria included the presence of CNS disease, creatinine clearance (CrCl) < 30 mL/min, eligibility for HDT-ASCT or allogeneic stem-cell transplantation per investigator decision, corticosteroids ≤ 1 week (> 10 mg per day prednisone or equivalent), unwillingness to receive contraception or prophylaxis for deep vein thrombosis, desquamating rash with prior thalidomide, prior exposure to lenalidomide, chemotherapy ≤ 2 weeks, nitrosourea ≤ 6 weeks, monoclonal antibody ≤ 8 weeks, radioimmunoconjugate ≤ 12 weeks, or external radiotherapy ≤ 3 weeks.

Study Design

MCL-001 (EMERGE; NCT00737529) was a global, multicenter, single-arm, open-label phase II study of safety and efficacy of single-agent lenalidomide in patients who had relapsed, progressed, or were refractory to bortezomib. Primary end points were ORR and DOR; secondary end points included safety, CR/CRu, time to response (TTR), time to progression (TTP), time to treatment failure (TTF), PFS, and OS.

Lenalidomide 25 mg (10 mg for CrCl ≥ 30 to < 60 mL/min) was self-administered orally on days 1 through 21 of each 28-day cycle until PD, intolerance, or voluntary withdrawal. Dosing was based on prior NHL studies (including MCL)[35-37] and approved dosing in multiple myeloma.[39]

Dose modification/interruption was planned in the event of grade ≥ 2 allergic reaction or hypersensitivity; > 3× upper limit of normal AST, ALT, or bilirubin; grade I or higher tumor lysis syndrome (TLS; by Cairo-Bishop grading system[40]); sustained grade ≥ 3 neutropenia for ≥ 7 days or associated with fever (≥ 38.5°C); thrombocytopenia (platelets < 50,000/μL); constipation; desquamating (blistering) rash (or grade 4 nondesquamating rash); venous thrombosis/embolism; new peripheral neuropathy; tumor flare reaction (TFR); or lenalidomide-related nonhematologic AE. Allopurinol 300 mg per day or equivalent was recommended for TLS prophylaxis with oral hydration during the first 7 days of treatment (or as indicated). Patients at high-risk for developing a thromboembolic event (TEE; defined as a history of TEE and/or concomitant medication with increased risk and/or known hypercoagulable state regardless of thromboembolic history) received prophylaxis (eg, aspirin 70 to 100 mg per day, low-molecular-weight heparin [LMWH], or warfarin, per investigator). Growth factors were not administered as prophylaxis but were allowed to treat severe hematologic events. Concomitant anticancer therapy was prohibited, although physiologic doses of steroids (≤ 10 mg per day) not prescribed for MCL were permitted.

Response and Safety Assessments

Safety assessments included AEs, pregnancy tests for females of childbearing age, second primary malignancies (SPMs), TLS, and TFR, hematology, serum chemistry, and other laboratory tests. CT scans were performed every two cycles (± 7 days) throughout treatment and every 90 days (± 14 days) after stopping lenalidomide until progression or initiation of subsequent antilymphoma therapy. Confirmatory bone marrow aspirate and unilateral biopsy was required within 28 days for patients achieving CR (by CT).

Efficacy analyses were performed in the intent-to-treat patient population as defined in the protocol. Response data were evaluated by investigators and an independent review committee (ie, central review) per modified International Workshop Lymphoma Response Criteria.[24,41,42] Central reviewers prospectively reviewed efficacy data to provide an objective, unbiased independent review of clinical outcomes blinded to institution information, demographic information, and investigator assessments. Central reviewers consisted of four experts in radiology and hematology/oncology. Two radiologists first evaluated medical imaging data in a blinded independent radiology review, with adjudication by a third radiologist as needed, followed by an independent overall hematologist/oncologist review of radiology results in conjunction with pertinent clinical data to determine response. Central reviewers provided the primary efficacy results for this study.

Statistical Analyses

Primary efficacy end points were evaluated following six cycles (± 1 month) of lenalidomide or on treatment discontinuation. Patients discontinuing before achieving a response or who switched to another therapy were considered nonresponders. Response rates were calculated with two-sided

exact 95% CIs, with a requirement of > 15% responders to validate efficacy. Waterfall plots were evaluated for patients with baseline and postbaseline lesion assessments for a maximum percentage change from baseline in tumor burden for target lesions. DOR was calculated from the day of first response (of PR or better) to PD or last tumor assessment. The Kaplan-Meier product limit method estimated the survivorship function for all time-to-event end points (eg, DOR, PFS, OS) with median estimates and two-sided 95% CIs. Censoring rules followed regulatory guidance and were prespecified before database lock. AEs were assessed according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 3.0.

Exploratory subgroup analyses included ORR and DOR assessments per baseline demographics and prior therapies. Multivariate logistic regression models evaluated possible baseline and prognostic factors predictive of response. Results were reported with a cutoff date of July 2, 2012, with continued follow-up until 70% patients had died or to a maximum of 4 years from last patient enrollment. All *P* values reported were two-sided.

RESULTS

Patient Characteristics

From January 2009 to July 2012, 134 patients at 45 study sites worldwide received one or more doses of lenalidomide. Median age was 67 years and 63% of patients were age 65 years or older (Table 1). Almost all patients (93%) had stage III to IV MCL, 57% had high tumor burden, 33% had bulky disease, and one-third had prior HDT-ASCT. In addition to study-required prior therapies, other prior treatments included vincristine (96%), glucocorticoids (92%), cytarabine (44%), etoposide (40%), bendamustine (25%), and platinum compounds (25%).

Table 1. Patient Demographics, Baseline Disease Characteristics at Time of Study Entry, and Prior Antilymphoma Treatment (N = 134)

Characteristic	No. of Patients	%	Median	Range
Age, years			67	43-83
≥ 65	85	63		
Male	108	81		
Stage III to IV	124	93		
ECOG PS				
0-1	116	87		
2	18	13		
Moderate-severe renal insufficiency*	29	22		
Time from original MCL diagnosis to enrollment, years				
< 3	52	39		
≥ 3	82	61		
MIPI score group at enrollment				
Intermediate	51	38		
High	39	29		
Positive bone marrow involvement†	55	41		
High tumor burden‡	77	57		
Bulky disease§	44	33		
No. of prior treatment regimens			4	2-10
No. of prior systemic antilymphoma therapies				
2	29	22		
3	34	25		
≥ 4	71	53		
Received prior bortezomib	134	100		
Refractory to prior bortezomib	81	60		
Refractory to last therapy	74	55		
Received prior high-dose or dose-intensive therapy‖	44	33		
Received prior bone marrow or autologous stem cell transplantation	39	29		
Time from last prior systemic antilymphoma therapy, months			3.1	0.3-37.7
< 6	96	72		
≥ 6	38	28		

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; MCL, mantle cell lymphoma; MIPI, MCL International Prognostic Index.

*Moderate renal insufficiency defined as creatinine clearance (CrCl) ≥ 30 and < 60 mL/min; severe renal insufficiency defined as CrCl < 30 mL/min.

†Bone marrow involvement was not required per protocol; prior data for bone marrow biopsy and aspirate were collected in 115 evaluable patients.

‡Defined as at least one lesion ≥ 5 cm in diameter or three or more lesions that were ≥ 3 cm in diameter by central radiology review.

§Defined as at least one lesion ≥ 7 cm in diameter by central radiology review.

‖Includes stem cell transplantation, hyper-CVAD (fractionated cyclophosphamide, vincristine, doxorubicine, dexamethasone), or R-hyper-CVAD (rituximab plus hyper-CVAD).

Efficacy

ORR by central review was 28% (95% CI, 20% to 36%; Table 2). The CR/CRu rate was 7.5% (95% CI, 4% to 13%). Responders showed a median DOR of 16.6 months (95% CI, 7.7 to 26.7 months; Fig 1), and median duration of CR/CRu of 16.6 months (95% CI, 16.6 months to not reached). At data cutoff, 18 patients had a DOR ≥ 6 months and 10 patients had a DOR ≥ 12 months (maximum DOR, 29.2+ months). Eleven of 39 patients maintained stable disease for ≥ 6 months, including four patients with stable disease for ≥ 12 months. Of note, efficacy results were similar for investigator assessments.

The median TTR was 2.2 months (3.7 months for CR/CRu), with 16 (43%) of 37 responders achieving at least PR by the first assessment (56 ± 7 days). Most responses were reported after two to four cycles of lenalidomide, although in some patients, up to 13 months of treatment was required to achieve best response. Reduction in tumor burden was based on maximum percentage change from baseline for target lesions by central review (Appendix Fig A1, online only). For 111 patients with baseline and postbaseline data available, 77 (69%) experienced a reduction, including 46 (41%) with a ≥ 50% reduction in tumor burden. Efficacy assessments using the waterfall plot calculated reductions in tumor burden that may not have met the stringent criteria for response even though there was a ≥ 50% reduction of all target lesions.

Median PFS was 4.0 months (95% CI, 3.6 to 5.6 months; Table 2 and Fig 1); median TTP and TTF were 5.4 months (95% CI, 3.7 to 7.5 months) and 3.8 months (95% CI, 2.3 to 4.5 months), respectively. With a median follow-up of 9.9 months, median OS was 19.0 months (95% CI, 12.5 to 23.9 months; Fig 1).

At data cutoff, 112 patients (84%) were off treatment and 22 (16%) continued treatment. Sixty-two patients (46%) received subsequent antilymphoma therapy following lenalidomide, with 13% ORR (eight of 62 patients) reported to date. The most common antilymphoma treatment following lenalidomide included rituximab alone (n = 5), rituximab/bendamustine (rituximab/bendamustine ± prednisone; n = 11), rituximab/bendamustine plus other chemotherapy/steroids (n = 12), and radiotherapy (n = 8). Four patients received lenalidomide following study completion (including one patient who discontinued therapy because of lack of PD postbortezomib, one with prolonged treatment delay in lenalidomide due to cytopenia, and two

Table 2. Efficacy Outcomes With Lenalidomide in Patients With Relapsed/Refractory MCL (N = 134)

Efficacy Parameter	Central Review			Investigator Review		
	No.	%	95% CI	No.	%	95% CI
ORR	37	28		43	32	
CR/CRu	10	7.5		22	16	
PR	27	20		21	16	
SD	39	29		36	27	
PD	35	26		43	32	
Missing response assessment*	23	17		12	9	
Median DOR, months	16.6		7.7 to 26.7	18.5		12.8 to 26.7
Median duration of CR/CRu, months	16.6		16.6 to N/R	26.7		26.7 to N/R
Median duration of PR, months	9.2		5.7 to 20.5	7.7		3.7 to 21.4
TTR, months						
Median	2.2			2.0		
Range	1.7-13.1			1.7-15.9		
Time to CR/CRu, months						
Median	3.7			5.6		
Range	1.9-29.5			1.8-24.2		
Median PFS, months	4.0		3.6 to 5.6	3.8		3.5 to 6.8
Median TTP, months	5.4		3.7 to 7.5	4.0		3.6 to 7.5
Median TTF months	3.8		2.3 to 4.5	3.8		2.3 to 4.5
Median OS, months	19.0		12.5 to 23.9	19.0		12.5 to 23.9

Abbreviations: CR, complete response; CRu, unconfirmed complete response; DOR, duration of response; MCL, mantle cell lymphoma; ORR, overall response rate; OS, overall survival; N/R, not reached; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TTF, time to treatment failure; TTP, time to progression; TTR, time to response.

*Includes patients without or with incomplete postbaseline response assessment. For these 23 patients, the investigator's assessment for best ORR included 12 with progressive disease, 10 not assessable, and one CR (no identifiable target lesions by the central radiology reviewer who reported this patient as not evaluable, although a single GI [colon] lesion was reported by investigator readings). All 23 patients were included in the centrally reviewed response assessments as nonresponders.

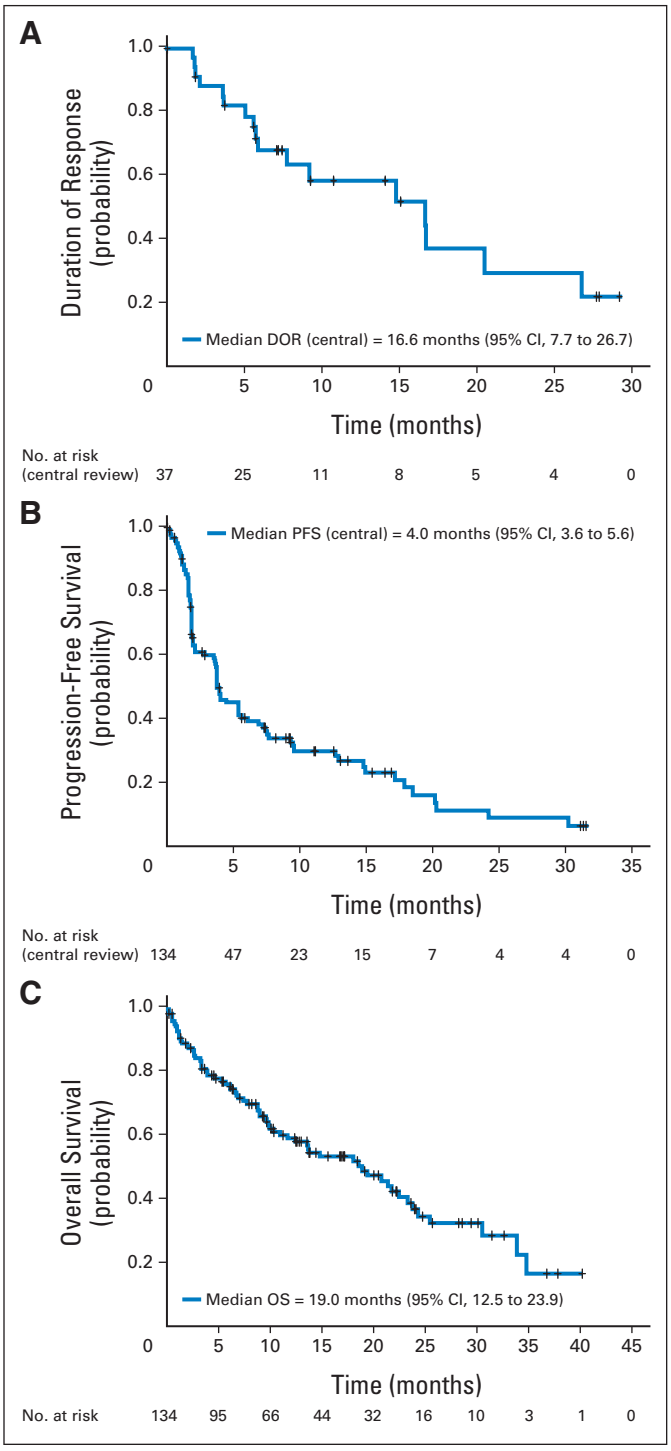

Fig 1. Duration of (A) response (DOR), (B) progression-free survival (PFS), and (C) overall survival (OS) after lenalidomide in relapsed/refractory mantle-cell lymphoma (by central review).

patients who were given lenalidomide as subsequent therapy following PD).

Response by Subgroup Analysis

Lenalidomide showed consistent ORR and DOR across subgroups (Table 3). Multivariate logistic regression analysis (central review) evaluated factors including demographic characteristics, baseline disease characteristics, number of and response to prior therapies, and the starting dose of lenalidomide. The only factor that was significant in both the univariate and multivariate models was high lactate dehydrogenase at baseline.

Safety

The average daily dose of lenalidomide was 20 mg per day (± 6.5 mg per day [standard deviation]) received for a median duration of 95 days (range, 1 to 1,002 days). Fifty-eight percent of patients received three or more cycles of lenalidomide, 40% received six or more cycles, and 19% received 12 or more cycles. Dose interruptions were present in 57% of patients; median time to first dose interruption was 29 days (ie, after one cycle) with a median time to resume lenalidomide of 7 days (range, 1 to 59 days). Dose reductions due to AEs were reported in 51 patients (38%), with a median time to first dose reduction of 57 days (ie, after two cycles). Twenty-six patients (19%) discontinued lenalidomide due to AEs. The most common AEs leading to dose reductions, interruptions, or discontinuations were neutropenia and thrombocytopenia.

Ninety-nine percent of patients experienced at least one AE, including 66% grade ≥ 3 (Table 4). The most common grade ≥ 3 AEs

Table 3. Summary of Subgroup Analyses of ORR and DOR by Baseline Demographics and Patient Characteristics With Lenalidomide in Evaluable Patients With Relapsed/Refractory MCL (central review)

Characteristic	Total No. of Patients	ORR			DOR		
		No.	%	95% CI	No.	Median	95% CI
Median age, years							
< 65	49	15	31	18 to 45	15	20.5	5.6 to N/A
≥ 65	85	22	26	17 to 37	22	9.2	5.8 to 16.7
Sex							
Male	108	28	26	18 to 35	28	16.7	9.2 to N/A
Female	26	9	35	17 to 56	9	7.7	2.1 to 20.5
ECOG PS							
0-1	116	31	27	19 to 36	31	16.7	14.8 to N/A
2-4	18	6	33	13 to 59	6	7.7	1.7 to 9.2
Renal function							
Normal	99	28	28	20 to 38	28	20.5	5.7 to N/A
Moderate insufficiency	28	7	25	11 to 45	7	9.2	7.7 to 16.6
Time from MCL diagnosis to first dose, years							
< 3	52	12	23	13 to 37	12	16.6	5.1 to N/A
≥ 3	82	25	31	21 to 42	25	14.8	5.8 to 20.5
MCL (Ann Arbor) stage							
I or II	10	1	10	0.3 to 45	1	7.7	N/A
III or IV	124	36	29	21 to 38	36	16.6	9.2 to 26.7
MIPI score at enrollment							
Low	39	14	36	21 to 53	14	20.5	5.6 to N/A
Intermediate	51	12	23	13 to 38	12	16.7	5.7 to 26.7
High	39	10	26	13 to 42	10	7.7	3.6 to N/A
LDH							
Normal	84	32	38	28 to 49	32	16.7	14.8 to N/A
High	47	5	11	4 to 23	5	5.8	1.7 to 7.7
WBC count ($\times 10^9$/L)							
< 6.7	67	22	33	22 to 45	22	14.8	5.6 to 20.5
6.7 to < 10	41	7	17	7 to 32	7	26.7	7.7 to N/A
10 to < 15	9	6	67	30 to 93	6	N/A	3.6 to N/A
≥ 15	12	1	8	0.2 to 39	1	N/A	N/A to N/A
Tumor burden							
High*	77	22	29	19 to 40	22	14.8	5.8 to 26.7
Low	54	15	28	17 to 42	15	16.6	5.6 to 16.6
Bulky disease							
Yes†	44	13	30	17 to 45	13	14.8	5.7 to N/A
No	87	24	28	19 to 38	24	16.6	5.8 to N/A
Prior bone marrow involvement‡							
Positive	55	13	24	13 to 37	13	9.2	3.6 to N/A
Negative	52	13	25	14 to 39	13	16.7	5.1 to N/A
Indeterminate	8	4	50	16 to 84	4	14.8	N/A to N/A
No. of prior systemic antilymphoma therapies							
< 3	29	9	31	15 to 51	9	16.6	7.7 to N/A
≥ 3	105	28	27	19 to 36	28	16.7	5.7 to 26.7
Received prior stem cell transplantation							
Yes	39	12	31	17 to 48	12	16.7	3.6 to 16.7
No	95	25	26	18 to 36	25	14.8	5.8 to 26.7
Received prior high-intensity therapy							
Yes	44	12	27	15 to 43	12	16.7	3.6 to 16.7
No	90	25	28	19 to 38	25	14.8	5.8 to 26.7
Time from last prior systemic antilymphoma therapy, months							
< 6	96	23	24	16 to 34	23	7.7	3.6 to 26.7
≥ 6	38	14	37	22 to 54	14	16.7	14.8 to N/A
Relapsed/refractory to prior bortezomib							
Refractory	81	22	27	18 to 38	22	20.5	7.7 to N/A
Relapsed/progressed	51	15	29	18 to 44	15	16.6	5.1 to 16.7
Relapsed/refractory to last prior therapy							
Refractory	74	20	27	17 to 39	20	26.7	5.6 to N/A
Relapsed/progressed	53	16	30	18 to 44	16	14.8	5.7 to 20.5

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