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Joshua N. Gustine, Raphael E. Szalat, Andrew Staron, Tracy Joshi, Lisa Mendelson, J. Mark Sloan, Vaishali Sanchorawala.

Amyloidosis Center and Section of Hematology and Medical Oncology, Boston University School of Medicine and Boston Medical Center, Boston, MA, USA.

Corresponding Author:
Vaishali Sanchorawala, MD
Amyloidosis Center
Boston University School of Medicine
72 East Concord Street, K-503, Boston, MA 02118
Phone: (617) 358-4750 Fax: (617) 358-4735
Email: vaishali.sanchorawala@bmc.org

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Light chain (AL) amyloidosis is an uncommon clinical manifestation of Waldenström macroglobulinemia (WM), an IgM-secreting lymphoplasmacytic lymphoma (LPL) characterized by recurrent mutations in MYD88 and CXCR4. WM-associated AL amyloidosis (WM-AL) is distinct from typical AL amyloidosis not only on the basis of its underlying lymphoplasmacytic neoplastic clone, but also the absence of t(11;14) and higher rates of soft tissue, lymph node, lung, and peripheral nerve involvement.[1,2] The occurrence of WM-AL amyloidosis confers a worse prognosis in WM patients,[3] and the management approach is not standardized. Commonly used treatment regimens are derived from WM without concurrent AL amyloidosis or typical AL amyloidosis with a pure plasma cell neoplastic clone.[4-6] We sought to describe the treatment and survival outcomes in a cohort of patients with WM-AL amyloidosis.

We identified consecutive patients with WM-AL amyloidosis evaluated at the Boston University (BU) Amyloidosis Center between 2006 and 2022. All patients met consensus clinicopathological criteria for a diagnosis of WM (i.e., presence of a serum IgM paraprotein and bone marrow [BM] infiltration by LPL of any size)[7] and had positive Congo red staining of a biopsy specimen with typing confirming AL amyloidosis. Typing of the amyloidogenic protein was performed by immunohistochemistry, immunogold electron microscopy, or liquid chromatography and tandem mass spectrometry. Hematologic and organ responses to treatment for AL amyloidosis and WM were assessed using consensus definitions.[8,9] Event-free survival (EFS) was defined as the time between WM-AL amyloidosis diagnosis among treated patients and next line of treatment or death, whichever occurred first. Overall survival (OS) was defined as the time between WM-AL amyloidosis diagnosis and death from any cause or last follow-up. Logistic regression models were fitted to identify predictors of

hematologic response. Time-to-event outcomes were calculated using the Kaplan-Meier method, and the log-rank test was used to compare estimates between groups. The Cox-proportional hazard regression method was used to fit models for EFS and OS. P-values <0.05 were considered statistically significant.

Forty-nine patients with WM-AL amyloidosis comprised the study cohort. Ten patients (20%) were simultaneously diagnosed with WM and AL amyloidosis. The remaining 39 patients (80%) had AL amyloidosis diagnosed after WM, with a median time to diagnosis of 3 months (range, 0-201); 12 patients (24%) were diagnosed >5 years after WM. Eight patients (16%) received a median of 2 WM-directed therapies (range, 1-4) before the diagnosis of AL amyloidosis. Baseline clinical characteristics at the time of WM-AL amyloidosis diagnosis are shown in **Table 1**. The presenting symptoms were heterogeneous and included: peripheral edema (n=14; 29%), dyspnea (n=8; 17%), paresthesia (n=7; 14%), syncope (n=5; 10%), pleural effusion (n=5; 10%), diarrhea (n=4; 8%), foamy urine (n=4; 8%), carpal tunnel syndrome (n=3; 6%), atrial fibrillation (n=3; 6%), acute kidney injury (n=3; 6%), periorbital ecchymosis (n=2; 4%), macroglossia (n=2; 4%), lymphadenopathy (n=2; 4%), and subcutaneous mass (n=2; 4%).

Forty-four patients (90%) received at least one treatment after the diagnosis of WM-AL amyloidosis; 5 patients did not receive treatment due to poor performance status and/or patient preference (**Table 2**). Hematologic response assessments using serum free light chain (FLC) and IgM levels were available for 43 of 44 patients. Based on FLC criteria, the overall (ORR), complete (CR), very good partial response (VGPR), and partial response (PR) rates were 77%, 26%, 26%, and 26%, respectively. Based on IgM criteria, the ORR, CR,

VGPR, PR, and minor response (MR) rates were 86%, 26%, 26%, 27%, and 7%, respectively. There was discordance between FLC and IgM categorical responses (PR or better) in 6 of 43 patients (14%); 3 patients had deeper categorical responses by IgM criteria, while another 3 patients had deeper categorical responses by FLC criteria. No baseline clinical factors were associated with achieving a hematologic CR/VGPR by either FLC or IgM criteria ($p>0.05$ for all comparisons). Cardiac, renal, and hepatic organ response rates were 67% (n=6/9), 52% (n=12/23), and 67% (n=2/3), respectively. Patients with a hematologic CR/VGPR had significantly higher organ response rates by both FLC (78% vs. 17%; $p=0.002$) and IgM criteria (83% vs. 9%; $p<0.001$).

After a median follow-up of 2.6 years (95% CI 1.6-5.2), 21 patients (43%) had died. The median EFS was 4.9 years (95% CI 2.3-not reached [NR]), and the estimated 5-year EFS rate was 48% (**Figure 1A**). The median OS was 7.3 years (95% CI 5.4-NR), and the estimated 5-year OS rate was 70% (**Figure 1B**). A baseline serum creatinine >2.0 mg/dL was independently associated with both a shorter EFS (0.7 vs. 6.1 years; HR 4.20, 95% CI 1.51-11.7; $p=0.003$) and OS (2.5 vs. 10 years; HR 3.91, 95% CI 1.29-11.8; $p=0.02$) (**Table S1** and **Figure S1**). There was also a trend toward shorter OS with a BNP >81 pg/mL (5.2 vs. 10 years; HR 2.31, 95% CI 0.93-5.77; $p=0.07$; **Table S1** and **Figure S1**). Using the BU cardiac staging system, patients with stage I, II, and III disease had 5-year OS estimates of 81%, 61%, and 25%, respectively ($p=0.10$; **Figure S1**). The depth of hematologic FLC and IgM response was significantly associated with both EFS and OS (**Figures 1C-F**). The median OS from the time of WM diagnosis was 12.8 years (95% CI 10.8-NR).

The response and survival outcomes for each frontline treatment regimen are summarized in **Table 2**. Maintenance rituximab was administered in 7 of 33 patients (21%) who achieved a PR or better to a rituximab-containing frontline regimen. Among these patients, maintenance rituximab was associated with a significantly longer 5-year EFS (100% vs. 41%; p=0.02) and a trend for longer OS (100% vs. 67%; p=0.05) (**Figure S1**).

Eleven of 44 treated patients (25%) received salvage therapy, which most commonly was a bortezomib- and/or bendamustine-based regimen (**Table S2**). Two patients received ibrutinib monotherapy without achieving either a hematologic or organ response. One patient was treated with venetoclax-obinutuzumab after being refractory to bortezomib, dexamethasone, and rituximab (BDR) and bendamustine and rituximab (Benda-R), and achieved a hematologic PR with stable proteinuria.

The occurrence of WM-AL amyloidosis is an uncommon complication that alters the natural history of WM. We observed a median OS of 7.3 years from the diagnosis of WM-AL amyloidosis. This survival estimate compares favorably to the median OS of 2.5 years published by the Mayo Clinic,[3] perhaps due to a lower frequency of cardiac involvement in our patient cohort (35% vs. 57%). Both studies identified cardiac involvement as an adverse prognostic factor for OS, suggesting the potential relevance of the BU and Mayo cardiac staging systems in patients with WM-AL amyloidosis. We also identified renal dysfunction as an important prognostic factor for both EFS and OS. In contrast to the study by the Mayo Clinic group,[3] we included patients with BM involvement by LPL <10% according to the consensus diagnostic criteria for WM.[7] This difference in study design is unlikely to explain the observed survival discrepancy, as BM involvement by LPL (<10% vs. ≥10%) was not

prognostic for survival. Importantly, we show that the established response criteria for both AL amyloidosis and WM are prognostic for survival and predictive of organ response in patients with WM-AL amyloidosis.[8,9]

We also described the timing of diagnosis of AL amyloidosis in WM patients. In most cases, AL amyloidosis was diagnosed within a few months of WM; however, 24% of patients were diagnosed >5 years later. This could be due to delayed recognition of the clinical syndrome of amyloidosis or AL amyloidosis may be a late complication in some cases of WM. Nevertheless, our finding highlights the importance of monitoring for red flag symptoms of AL amyloidosis in WM patients throughout the entire disease course. In particular, cardiac AL amyloidosis should be considered in WM patients on BTK inhibitors who develop atrial fibrillation, a well-recognized side effect. In one series, approximately 8% of WM patients who developed atrial fibrillation on ibrutinib had underlying cardiac AL amyloidosis.[10] AL amyloidosis should also be considered in the differential diagnosis of IgM monoclonal gammopathy of unknown significance in the appropriate clinical scenario, particularly given the lower serum IgM levels we observed in patients with WM-AL amyloidosis.

Prospective data to define the optimal treatment regimen for WM-AL amyloidosis are lacking. Our findings demonstrate that standard WM regimens such as BDR or Benda-R can also be effective in WM-AL amyloidosis. Previous studies describing Benda-R in patients with IgM-AL amyloidosis did not delineate outcomes based on the underlying neoplastic clone.[4,5] We report deep and durable responses with frontline use of HDM/SCT, which is typically reserved for the salvage setting in WM. HDM/SCT should be considered in selected patients with WM-AL amyloidosis, particularly since HDM/SCT can induce prolonged survival (>20 years) in

typical AL amyloidosis.[11] We also observed improved EFS with maintenance rituximab. Maintenance rituximab is not routinely used in WM based on the MAINTAIN trial,[6] but our data suggest it may have a role in WM-AL amyloidosis for patients who respond to induction therapy. Venetoclax represents a novel treatment option for WM,[12] and we present the first published case in a patient with WM-AL amyloidosis. Unlike in WM, ibrutinib is associated with mixed efficacy and tolerability in WM-AL amyloidosis and must be used with caution, particularly in patients with cardiac involvement given its pro-arrhythmic properties.[13,14] Second-generation BTK inhibitors like zanubrutinib, which have less cardiotoxicity than ibrutinib, warrant further investigation in WM-AL amyloidosis. Finally, there is currently no data on daratumumab in patients with WM-AL amyloidosis, but a phase 2 trial in WM was stopped due to futility.[15]

Limitations of this study include the inherent selection bias associated with a non-randomized, observational study from a tertiary referral center. However, this study is the largest to date describing treatment outcomes in patients with WM-AL amyloidosis. Prospective studies are needed to optimize the management of patients with WM-AL amyloidosis.

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Table 1. Baseline clinical characteristics at the time of AL amyloidosis diagnosis in patients with Waldenström macroglobulinemia.

Patient Characteristic	**All Patients (N=49)**
Age, years	
Median (range)	68 (56-86)
>65 years, n/N (%)	30/49 (61%)
Sex, n (%)	
Male	27/49 (55%)
Female	21/49 (45%)
Light chain isotype, n (%)	
Kappa	19/49 (39%)
Lambda	30/49 (61%)
Hemoglobin level	
Median (range)	12.4 (9.2-18.1)
≤11.5 g/dL, n (%)	13/48 (27%)
Platelet count	
Median (range)	263 (126-652)
≤100 K/uL, n (%)	0/48 (0%)
Beta2-microglobulin level	
Median (range)	3.2 (1.6-22.2)
>3 mg/L, n (%)	26/48 (54%)
Serum IgM level	
Median (range)	1418 (284-5498)
>4000 mg/dL, n (%)	6/49 (12%)
dFLC, mg/L	
Median (range)	73.7 (5.1-1333.5)
>180 mg/L, n (%)	10/49 (20%)
Bone marrow involvement by LPL	
Median (range)	20 (10-60)
>10%, n (%)	41/48 (85%)
Tumor genotype, n (%)	
MYD88 mutation	17/21 (81%)
CXCR4 mutation	3/9 (33%)
t(11;14)	0/27 (0%)
Serum creatinine, mg/dL	
Median (range)	0.9 (0.5-4.9)
>2.0 mg/dL, n (%)	7/48 (15%)
Urine protein excretion, mg/24hr	
Median (range)	655 (0-14,064)
>5000 mg/24hr, n (%)	13/48 (27%)
Alkaline phosphatase, IU/L	
Median (range)	91 (36-924)
>150 IU/L, n (%)	8/47 (17%)
Brain natriuretic peptide, pg/mL	
Median (range)	77 (3-2163)
>81 pg/mL, n (%)	23/48 (48%)

N-terminal pro-brain natriuretic peptide, pg/mL	
Median (range)	554 (62-5732)
>332 pg/mL, n(%)	13/22 (59%)
Troponin I, ng/mL	
Median (range)	0.012 (0.006-0.599)
>0.1 ng/mL	4/48 (8%)
BU Cardiac Stage, n (%)	
I	25/48 (52%)
II	19/48 (40%)
III	4/48 (8%)
IPSSWM Stage, n (%)	
Low	12/48 (25%)
Intermediate	31/48 (65%)
High	5/48 (10%)
Organ Involvement, n (%)	
Renal	25/49 (51%)
Cardiac	17/49 (35%)
Peripheral nervous system	16/49 (33%)
Autonomic nervous system	10/49 (20%)
Gastrointestinal	8/49 (16%)
Lymph node	8/49 (16%)
Pulmonary	7/49 (14%)
Skin/soft tissue	7/49 (14%)
Hepatic	3/49 (6%)

dFLC, difference between the involved and uninvolved serum free light chain; LPL, lymphoplasmacytic lymphoma; BU, Boston University; IPSSWM, International Prognostic Scoring System for Waldenström's Macroglobulinemia.

Table 2. Clinical outcomes based on frontline regimen used for patients with AL amyloidosis associated with Waldenström macroglobulinemia.

Treatment Regimen	N	FLC Response, n/N		IgM Response, n/N		Organ Response, n/N[#]		Survival, median years (5-year survival, %)	
		ORR (≥PR)	≥VGPR	ORR (≥MR)	≥VGPR	Cardiac	Renal	EFS	OS
Benda-R	15	12/15 (80%)	8/15 (53%)	15/15 (100%)	10/15 (67%)	3/4 (75%)	5/6 (83%)	5.4 (65%)	7.3 (86%)
BDR	9	6/9 (67%)	6/9 (67%)	7/9 (78%)	3/9 (33%)	1/2 (50%)	2/6 (33%)	4.4 (48%)	7.3 (57%)
HDM/SCT*	9	9/9 (100%)	8/9 (89%)	9/9 (100%)	8/9 (89%)	2/2 (100%)	5/6 (83%)	NR (88%)	NR (86%)
CPR	5	3/5	1/5	4/5	1/5	--	0/2	1.7	12.0
CyBorD±R	2	2/2	0/2	2/2	0/2	--	0/2	0.7	2.5
Melphalan	2	1/2	0/2	0/2	0/2	--	0/1	2.8	7.7
Rituximab	1	0/1	0/1	0/1	0/1	--	--	1.3	1.6
Flu-R	1	0/1	0/1	0/1	0/1	0/1	--	0.9	1.2

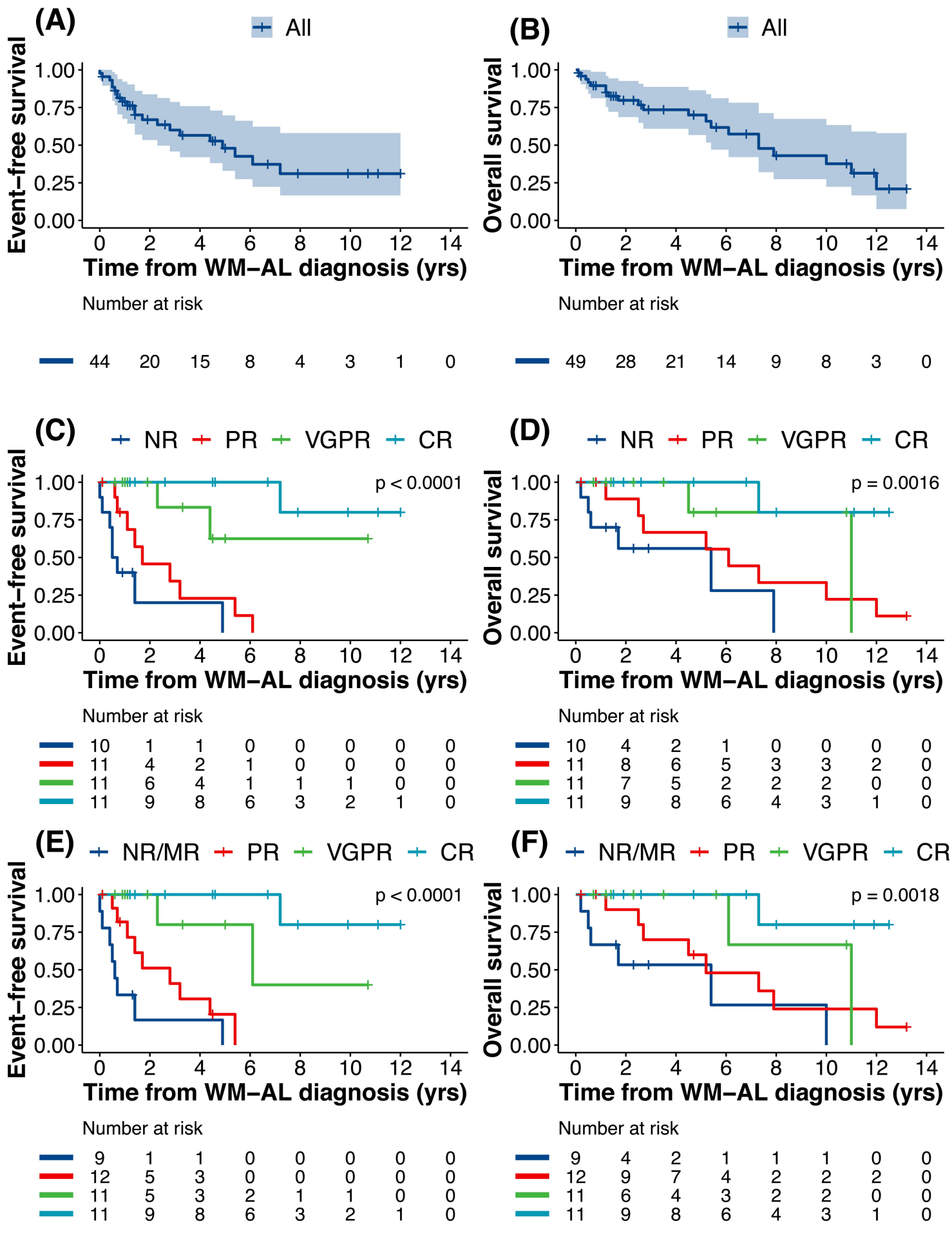
*All patients treated with HDM/SCT received pre-transplant induction therapy (BDR: n=8; Benda-R: n=1). Patients treated with HDM/SCT had an estimated EFS of 88% at both 5 and 10 years, and there was no 100-day treatment-related mortality.

[#]N signifies the total number of patients with involvement of the respective organ.

Benda-R, bendamustine and rituximab; BDR, bortezomib, dexamethasone, and rituximab; HDM/SCT, high-dose melphalan and stem cell transplantation; CPR, cyclophosphamide, prednisone, and rituximab; CyBorD±R, cyclophosphamide, bortezomib, dexamethasone, and rituximab; Flu-R, fludarabine and rituximab; FLC, free light chain; ORR, overall response rate; CR, complete response; VGPR, very good partial response; PR, partial response; MR, minor response; EFS, event free survival; OS, overall survival; NR, not reached.

FIGURE LEGEND

Figure 1. Survival in patients with AL amyloidosis associated with Waldenström macroglobulinemia. Kaplan-Meier survival curves for event-free survival (EFS) and overall survival (OS) for the entire cohort (A-B); EFS and OS stratified by depth of FLC response (C-D); and EFS and OS stratified by depth of IgM response (E-F). NR, no response; MR, minor response; PR, partial response; VGPR, very good partial response; CR, complete response.


(A)
All
Event−free survival
1.00
0.75
0.50
0.25
0.00
0 2 4 6 8 10 12 14
Time from WM−AL diagnosis (yrs)
Number at risk
44 20 15 8 4 3 1 0
(B)
All
Overall survival
1.00
0.75
0.50
0.25
0.00
0 2 4 6 8 10 12 14
Time from WM−AL diagnosis (yrs)
Number at risk
49 28 21 14 9 8 3 0
(C)
NR PR VGPR CR
p < 0.0001
Event−free survival
1.00
0.75
0.50
0.25
0.00
0 2 4 6 8 10 12 14
Time from WM−AL diagnosis (yrs)
Number at risk
10 1 1 0 0 0 0 0
11 4 2 1 0 0 0 0
11 6 4 1 1 1 0 0
11 9 8 6 3 2 1 0
(D)
NR PR VGPR CR
p = 0.0016
Overall survival
1.00
0.75
0.50
0.25
0.00
0 2 4 6 8 10 12 14
Time from WM−AL diagnosis (yrs)
Number at risk
10 4 2 1 0 0 0 0
11 8 6 5 3 3 2 0
11 7 5 2 2 2 0 0
11 9 8 6 4 3 1 0
(E)
NR/MR PR VGPR CR
p < 0.0001
Event−free survival
1.00
0.75
0.50
0.25
0.00
0 2 4 6 8 10 12 14
Time from WM−AL diagnosis (yrs)
Number at risk
9 1 1 0 0 0 0 0
12 5 3 0 0 0 0 0
11 5 3 2 1 1 0 0
11 9 8 6 3 2 1 0
(F)
NR/MR PR VGPR CR
p = 0.0018
Overall survival
1.00
0.75
0.50
0.25
0.00
0 2 4 6 8 10 12 14
Time from WM−AL diagnosis (yrs)
Number at risk
9 4 2 1 1 1 0 0
12 9 7 4 2 2 2 0
11 6 4 3 2 2 0 0
11 9 8 6 4 3 1 0

SUPPLEMENTAL APPENDIX

Table S1. Hazard regression analysis for event-free survival and overall survival to frontline treatment regimen in patients with WM-AL amyloidosis.

Event-Free Survival	**Univariate**		**Multivariate**	
Variables	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**
Age >65 years	0.81 (0.33-1.96)	0.64		
Male sex	1.43 (0.59-3.45)	0.43		
Lambda light chain isotype	1.21 (0.48-3.05)	0.67		
Hemoglobin ≤11.5 g/dL	1.09 (0.41-2.89)	0.86		
Platelet count ≤100 K/uL	UTC	UTC		
Beta2-microglobulin >3 mg/L	1.97 (0.74-5.23)	0.18		
Serum IgM >4000 mg/dL	0.33 (0.04-2.49)	0.28		
dFLC >180 mg/L	1.88 (0.68-5.23)	0.23		
BM involvement >10% by LPL	0.42 (0.15-1.18)	0.10		
MYD88 mutation	0.81 (0.08-7.84)	0.86		
Serum creatinine >2.0 mg/dL	**4.20 (1.52-11.7)**	**0.006**		
Urine protein >5000 mg/24hr	1.50 (0.61-3.73)	0.39		
ALP >150 IU/L	1.14 (0.33-3.94)	0.84		
BNP >81 pg/mL	1.56 (0.63-3.85)	0.33		
Troponin I >0.1 ng/mL	2.10 (0.47-9.29)	0.33		
Previously treated	0.91 (0.26-3.12)	0.88		
Overall Survival	**Univariate**		**Multivariate**	
Variables	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**
Age >65 years	1.07 (0.44-2.59)	0.88		
Male sex	2.27 (0.90-5.72)	0.08		
Lambda light chain isotype	1.75 (0.66-4.52)	0.25		
Hemoglobin ≤11.5 g/dL	1.08 (0.41-2.83)	0.88		
Platelet count ≤100 K/uL	UTC	UTC		
Beta2-microglobulin >3 mg/L	2.58 (0.98-6.78)	0.06		
Serum IgM >4000 mg/dL	0.46 (0.06-3.45)	0.45		
dFLC >180 mg/L	2.06 (0.78-5.43)	0.15		
BM involvement >10% by LPL	0.66 (0.22-2.01)	0.47		
MYD88 mutation	0.51 (0.08-3.14)	0.47		
Serum creatinine >2.0 mg/dL	**4.46 (1.63-12.2)**	**0.004**	**3.91 (1.29-11.8)**	**0.02**
Urine protein >5000 mg/24hr	0.94 (0.39-2.30)	0.90		
ALP >150 IU/L	**3.60 (1.19-10.9)**	**0.02**	2.59 (0.79-8.48)	0.11
BNP >81 pg/mL	**2.47 (1.03-5.94)**	**0.04**	2.31 (0.93-5.77)	0.07
Troponin I >0.1 ng/mL	2.16 (0.62-7.53)	0.23		
Previously treated	1.23 (0.42-3.93)	0.65		

Previously treated patients (n=8) received a WM-directed therapy before the diagnosis of AL amyloidosis. dFLC, difference between the involved and uninvolved serum free light chain; BM, bone marrow; LPL, lymphoplasmacytic lymphoma; ALP, alkaline phosphatase; BNP, brain natriuretic peptide; UTC, unable to calculate; OR, odds ratio; CI, confidence interval.

Table S2. Salvage treatment regimens utilized in patients with WM-AL amyloidosis.

Treatment Regimen	Number of Patients
BDR	4 (36%)
Benda-R	3 (27%)
CyBorD-R	2 (18%)
Ibrutinib	2 (18%)
CaRD	1 (9%)
Idelalisib	1 (9%)
Ven-O	1 (9%)

Eleven patients with WM-AL amyloidosis received salvage therapy. BDR, bortezomib, dexamethasone, and rituximab; Benda-R, bendamustine and rituximab; CyBorD-R, cyclophosphamide, bortezomib, dexamethasone, and rituximab; CaRD, carfilzomib, rituximab, and dexamethasone; Ven-O, venetoclax and obinutuzumab.

Figure S1. Survival in patients with WM-AL amyloidosis. Kaplan-Meier survival curves for event-free survival (EFS) and overall survival (OS) stratified by serum creatinine (A-B); OS stratified by BNP (C); OS stratified by BU cardiac staging system (D); and EFS and OS stratified by maintenance rituximab among patients who achieved a partial response or better to a rituximab-containing frontline regimen (E-F). BNP, brain natriuretic peptide.