

Gilead, and AbbVie and honoraria from Takeda, Ono, Janssen, Celgene, Bristol-Myers Squibb, and Novartis; R.U. had a consultancy with Mundipharma K.K., Ono Pharmaceutical Co., Ltd., and Terumo Co., Ltd., and received research funding from Kyowa Hakko Kirin Co., Ltd., Rikaken Co., Ltd., Medical & Biological Laboratories Co., Ltd., and Chugai Pharmaceutical Co., Ltd., and honoraria from Chugai Pharmaceutical Co., Ltd., Kyowa Hakko Kirin Co., Ltd., and Ono Pharmaceutical Co., Ltd.; and H.I. received research funding from Kyowa Hakko Kirin Co., Ltd., and honoraria from Kyowa Hakko Kirin Co., Ltd. The remaining authors declare no competing financial interests.

ORCID profiles: T.I., 0000-0002-1060-0777; H.I., 0000-0001-6157-636X.

Correspondence: Hiroshi Inagaki, Department of Pathology and Molecular Diagnostics, Graduate School of Medical Sciences, Nagoya City University, Nagoya 467-8601, Japan; e-mail: hinagaki@med.nagoya-cu.ac.jp.

## Footnotes

\*Y.S. and T.I. contributed equally to this study.

The online version of this article contains a data supplement.

## REFERENCES

- Uchiyama T, Yodoi J, Sagawa K, Takatsuki K, Uchino H. Adult T-cell leukemia: clinical and hematologic features of 16 cases. *Blood*. 1977;50(3):481-492.
- Ishitsuka K, Tamura K. Human T-cell leukaemia virus type I and adult T-cell leukaemia-lymphoma. *Lancet Oncol*. 2014;15(11):e517-e526.
- Matsuoka M, Jeang KT. Human T-cell leukaemia virus type 1 (HTLV-1) infectivity and cellular transformation. *Nat Rev Cancer*. 2007;7(4):270-280.
- Tsukasaki K, Utsunomiya A, Fukuda H, et al; Japan Clinical Oncology Group Study JCOG9801. VCAP-AMP-VECP compared with biweekly CHOP for adult T-cell leukemia-lymphoma: Japan Clinical Oncology Group Study JCOG9801. *J Clin Oncol*. 2007;25(34):5458-5464.
- Tsukasaki K, Hermine O, Bazarbachi A, et al. Definition, prognostic factors, treatment, and response criteria of adult T-cell leukemia-lymphoma: a proposal from an international consensus meeting. *J Clin Oncol*. 2009;27(3):453-459.
- Katsuya H, Yamanaka T, Ishitsuka K, et al. Prognostic index for acute- and lymphoma-type adult T-cell leukemia/lymphoma. *J Clin Oncol*. 2012;30(14):1635-1640.
- Fukushima T, Nomura S, Shimoyama M, et al. Japan Clinical Oncology Group (JCOG) prognostic index and characterization of long-term survivors of aggressive adult T-cell leukaemia-lymphoma (JCOG0902A). *Br J Haematol*. 2014;166(5):739-748.
- Yoshie O, Fujisawa R, Nakayama T, et al. Frequent expression of CCR4 in adult T-cell leukemia and human T-cell leukemia virus type 1-transformed T cells. *Blood*. 2002;99(5):1505-1511.
- Ishida T, Utsunomiya A, Iida S, et al. Clinical significance of CCR4 expression in adult T-cell leukemia/lymphoma: its close association with skin involvement and unfavorable outcome. *Clin Cancer Res*. 2003;9(10 Pt 1):3625-3634.
- Wong RWJ, Ngoc PCT, Leong WZ, et al. Enhancer profiling identifies critical cancer genes and characterizes cell identity in adult T-cell leukemia. *Blood*. 2017;130(21):2326-2338.
- Ishii T, Ishida T, Utsunomiya A, et al. Defucosylated humanized anti-CCR4 monoclonal antibody KW-0761 as a novel immunotherapeutic agent for adult T-cell leukemia/lymphoma. *Clin Cancer Res*. 2010;16(5):1520-1531.
- Ishida T, Joh T, Uike N, et al. Defucosylated anti-CCR4 monoclonal antibody (KW-0761) for relapsed adult T-cell leukemia-lymphoma: a multicenter phase II study. *J Clin Oncol*. 2012;30(8):837-842.
- Ishida T, Jo T, Takemoto S, et al. Dose-intensified chemotherapy alone or in combination with mogamulizumab in newly diagnosed aggressive adult T-cell leukaemia-lymphoma: a randomized phase II study. *Br J Haematol*. 2015;169(5):672-682.
- Nakagawa M, Schmitz R, Xiao W, et al. Gain-of-function CCR4 mutations in adult T cell leukemia/lymphoma. *J Exp Med*. 2014;211(13):2497-2505.
- Kataoka K, Nagata Y, Kitanaka A, et al. Integrated molecular analysis of adult T cell leukemia/lymphoma. *Nat Genet*. 2015;47(11):1304-1315.
- Yoshida N, Miyoshi H, Kato T, et al. CCR4 frameshift mutation identifies a distinct group of adult T cell leukaemia/lymphoma with poor prognosis. *J Pathol*. 2016;238(5):621-626.
- Shimoyama M. Diagnostic criteria and classification of clinical subtypes of adult T-cell leukaemia-lymphoma. A report from the Lymphoma Study Group (1984-87). *Br J Haematol*. 1991;79(3):428-437.
- Ishida T, Hishizawa M, Kato K, et al. Allogeneic hematopoietic stem cell transplantation for adult T-cell leukemia-lymphoma with special emphasis on preconditioning regimen: a nationwide retrospective study. *Blood*. 2012;120(8):1734-1741.
- Ogura M, Ishida T, Hatake K, et al. Multicenter phase II study of mogamulizumab (KW-0761), a defucosylated anti-CC chemokine receptor 4 antibody, in patients with relapsed peripheral T-cell lymphoma and cutaneous T-cell lymphoma. *J Clin Oncol*. 2014;32(11):1157-1163.
- Yano H, Ishida T, Inagaki A, et al. Defucosylated anti CC chemokine receptor 4 monoclonal antibody combined with immunomodulatory cytokines: a novel immunotherapy for aggressive/refractory Mycosis fungoides and Sezary syndrome. *Clin Cancer Res*. 2007;13(21):6494-6500.
- Mogamulizumab tops standard of care for CTCL. *Cancer Discov*. 2018;8(2):OF1.

DOI 10.1182/blood-2018-02-835991

© 2018 by The American Society of Hematology

## TO THE EDITOR:

# Treatment of IgM-associated immunoglobulin light-chain amyloidosis with rituximab-bendamustine

Richa Manwani, Sajitha Sachchithanantham, Shameem Mahmood, Darren Foard, Faye Sharpley, Tamer Rezk, Thirusha Lane, Cristina Quarta, Marianna Fontana, Helen J. Lachmann, Julian D. Gillmore, Carol Whelan, Philip N. Hawkins, and Ashutosh D. Wechalekar

National Amyloidosis Centre, University College London (Royal Free Campus), Rowland Hill Street, London, United Kingdom

Systemic amyloid light-chain amyloidosis (AL) is characterized by deposition of misfolded immunoglobulin light chains within organs. AL with an immunoglobulin M (IgM) monoclonal protein

(IgM-AL) accounts for 5% to 7% of AL and exhibits more prevalent lymph node, neuropathic, and lung involvement, less prevalent cardiac involvement, and lower amyloidogenic light chains.<sup>1</sup>

**Table 1. Baseline characteristics (N = 27)**

	Median (range) or n (%)
Median age (y)	70 (56-86)
Male:female	16 (59%):11 (41%)
<b>NYHA class</b>	
1	12 (44%)
2	14 (52%)
3	1 (4%)
4	0
<b>ECOG</b>	
0	7 (26%)
1	15 (56%)
2	5 (18%)
3	0
4	0
Cardiac involvement	17 (63%)
Median NT-pro-BNP (ng/L)	978 (42-5708)
Median cardiac troponin T (ng/L)	31.5 (3-122)
<b>Mayo stage</b>	
I	8 (30%)
II	13 (48%)
IIIA (NT-pro-BNP ≤8500 ng/L)	6 (22%)
IIIB (NT-pro-BNP >8500 ng/L)	0
Median systolic blood pressure (mmHg)	119 (100-164)
Median left ventricular wall thickness (mm)	11 (8.5-18)
Median LV ejection fraction (%)	60 (36-72)
Renal involvement	17 (63%)
Median serum creatinine (μmol/L)	98 (46-493)
Median GFR (mL/min)	68 (10-100)
Median proteinuria (g/24 h)	0.8 (0.1-34.6)
Liver involvement	6 (22%)
Median serum bilirubin (μmol/L)	6 (2-50)
Median ALP (U/L)	105 (25-1879)
Soft tissue involvement	2 (7%)
Peripheral nerve involvement	6 (22%)
Autonomic nerve involvement	4 (15%)
Lymph node involvement	13 (48%)
GI involvement	0
Median number of involved organs	1 (1-4)
<b>Involved light chains</b>	
κ	7 (26%)
λ	12 (44%)
No monoclonal light-chain excess	8 (30%)
Median dFLC (mg/L)	59.8 (2.2-856.4)
IgM κ M-protein, IgM λ M-protein	11 (44%), 14 (56%)
Median serum monoclonal protein (g/L)	11.5 (1-30)

ALP, alkaline phosphatase; dFLC, difference between involved and uninvolved light chains; ECOG, Eastern Cooperative Oncology Group; GFR, glomerular filtration rate; GI, gastrointestinal; LV, left ventricular; NT-pro-BNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association.

A reduction in intact monoclonal protein and free light chains is prognostic.<sup>1</sup> A very good partial response (VGPR) is associated with better survival and organ responses but is challenging to achieve because of an unclear underlying diagnosis (usually lymphoplasmacytic lymphoma) and lack of treatment uniformity. In a large retrospective study, we reported the use of 22 front-line regimens.<sup>1</sup> Rituximab-based regimens are often used alongside bortezomib, alkylators, or purine analogs; outcomes remain poor, with few complete responses.<sup>1-3</sup> Excellent hematological responses were reported in 12 IgM-AL patients treated with autologous stem cell transplantation,<sup>4</sup> but given the older age of IgM-AL patients, this is often not an option. Treatment of relapsed/refractory patients is particularly challenging, and recent experience with ibrutinib was disappointing.<sup>5</sup>

Bendamustine, which has features of an alkylator and purine analog, is used alongside rituximab in newly diagnosed and relapsed/refractory non-Hodgkin lymphoma<sup>6</sup> and in relapsed/refractory Waldenström macroglobulinemia, with an overall hematological response rate (ORR) of 83.3%.<sup>7</sup> Bendamustine in relapsed/refractory AL (with a plasma cell dyscrasia) resulted in disappointing responses.<sup>8</sup> There have been no studies focusing on the use of rituximab-bendamustine (BR) in IgM-AL. We report efficacy of BR in untreated and relapsed/refractory IgM-AL.

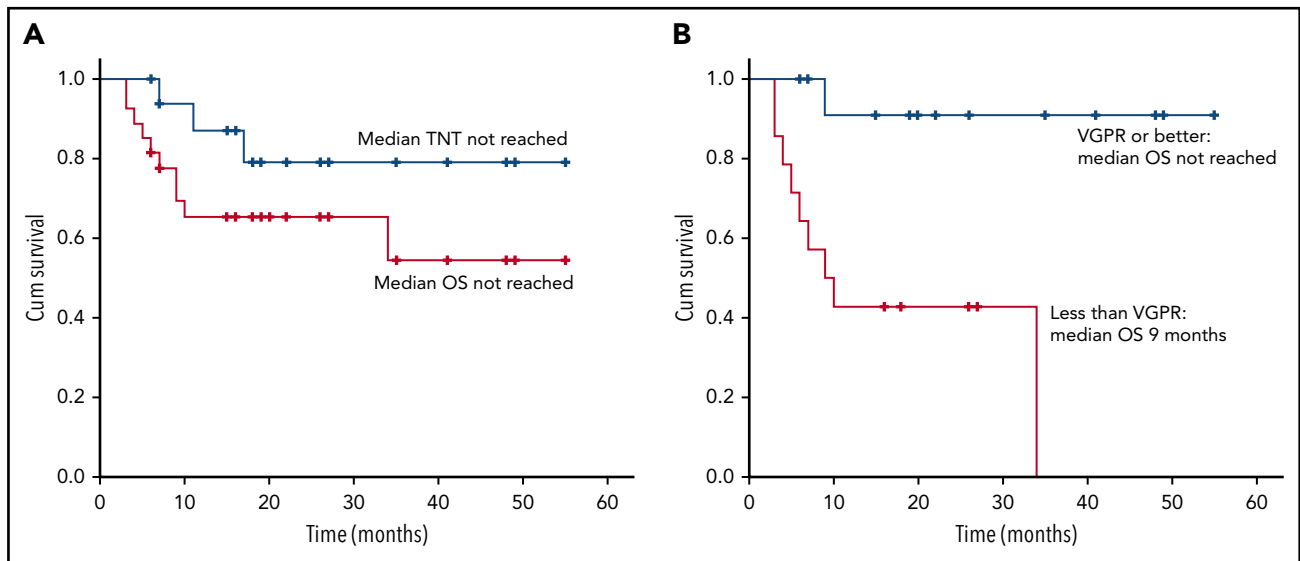
Twenty-seven patients treated with BR between 2011 and 2017 were identified from the UK National Amyloidosis Centre database; 22 received BR first-line therapy, 5 received BR second-line therapy. Twenty-five patients had a serum IgM M-protein. Two patients had lymphoplasmacytic lymphoma on bone marrow examination but had a serum IgG M-protein (instead of IgM).

AL was confirmed on biopsy immunohistochemistry or proteomic analysis. All patients underwent serial biochemical tests for organ function, cardiac biomarkers, serum free light chains, serum and urine protein electrophoresis and immunofixation, and echocardiography with or without cardiac magnetic resonance imaging (unless contraindicated). Organ involvement was defined by international amyloidosis consensus criteria.<sup>9</sup> Hematological responses were assessed according to AL amyloidosis response criteria.<sup>10</sup> In patients with nonevaluable serum free light chains (difference between involved and uninvolved light chains <50 mg/L), IgM M-protein was used for assessment.

Rituximab (375 mg/m<sup>2</sup>) was administered IV on day 1 as per local protocols. Bendamustine (90 mg/m<sup>2</sup>) was administered IV over 30 minutes on days 1 and 2. Four patients received additional corticosteroid therapy (3 received once-weekly dexamethasone [20 mg], and 1 received once-weekly dexamethasone [10 mg]). BR was repeated every 28 days.

Outcome variables were hematological and organ response, overall survival (OS), progression-free survival (PFS; progression defined as progression to next treatment or death), and time to next treatment (TNT).

Table 1 shows baseline characteristics. Median age was 70 years (56-86 years). Cardiac, renal, liver, peripheral nerve, autonomic nerve, and soft tissue involvement was found in 17 (63%), 17 (63%), 6 (22%), 6 (22%), 4 (15%), and 2 patients (7%), respectively. Lymphadenopathy was radiologically identified in 13 patients (48%); 7 patients (26%) had biopsy-proven lymph



**Figure 1. OS and TNT.** (A) OS on an ITT basis ( $n = 27$ ) and TNT on an evaluable basis ( $n = 17$ ). Median OS and median TNT were not reached. OS at 1 and 3 years was 65% and 56%, respectively. At 1 and 3 years, 88% and 79% of evaluable patients ( $n = 17$ ) had not progressed to further treatment. (B) Median OS was not reached in those patients who achieved a VGPR or better, with 92% alive at 2 years; median OS was 9 months in patients who did not achieve a VGPR. Cum survival, cumulative survival.

node amyloid deposition. The Mayo 2004 cardiac stage was I in 30% of patients, II in 48%, and III in 22%. Median M-protein was 11.5 g/L (1-30 g/L); 19 (70.4%) had evaluable free light chains. Of the remaining patients, all had an IgM M-protein ( $>5$  g/L) enabling response assessment.<sup>10</sup>

Twenty-one patients had available bone marrow data (trephine with or without flow cytometry; 3 normal, 1 plasma cell infiltration, 14 lymphoplasmacytic lymphoma, and 3 NHL not specifically classified). Five patients were treated with BR for refractory disease; previous therapies included bortezomib-cyclophosphamide-dexamethasone in 2 patients and rituximab-bortezomib-dexamethasone, rituximab-cyclophosphamide-vincristine-prednisolone, and rituximab-cyclophosphamide-dexamethasone in 1 case each.

The median number of BR cycles was 5 (range, 1-8). The median number of previous cycles in the second-line group was 6 (range, 4-8). Three patients received twice-monthly rituximab maintenance (375 mg/m<sup>2</sup> IV) after first-line therapy with BR. All 3 patients remain on rituximab maintenance, with treatment duration thus far of 8, 10, and 11 months.

ORR on an intention-to-treat (ITT) and evaluable basis was 59% and 76%, respectively. Hematological responses (ITT) were a complete response (CR) in 11% of patients, VGPR in 37%, partial response (PR) in 11%, and no response (NR) in 41% (including 22% deaths). In the first-line group, hematological responses were CR 14%, VGPR 32%, PR 14%, and NR 40% (including death in 18% of patients). The evaluable responses were CR 17%, VGPR 39%, PR 17%, and NR 27%. Of the 3 patients treated with twice-monthly rituximab maintenance, 1 remains in VGPR, 1 in CR (having been in VGPR at time of completing BR), and 1 in PR (nonresponder at time of BR completion). Among the 5 patients treated for refractory AL, 3 achieved a VGPR and 2 were nonresponders (including 1 death). Three out of 17 patients with cardiac involvement achieved N-terminal pro-brain natriuretic peptide responses, and 3 out of 17 patients achieved renal responses by consensus criteria.<sup>10</sup>

Median follow-up was 18 months (3-55 months). Median OS was not reached (Figure 1A). Median OS was not reached in patients who achieved VGPR or better (compared with 9 months in patients who did not) (Figure 1B). Median PFS was 34 months. Five patients (18.5%) died within 6 months of diagnosis (3 Mayo stage II and 2 stage III). On 6-month landmark analysis, median PFS was not reached. Of patients in the 6-month landmark analysis who achieved VGPR or better, median OS and PFS were not reached (compared with 34 and 11 months, respectively, in patients who did not). Three patients progressed to next treatment (their response to BR was VGPR, PR, and NR). Median TNT was not reached, with 88% and 79% of evaluable patients ( $n = 17$ ) not progressing to next treatment at 1 and 3 years, respectively (Figure 1A).

Grade 3-4 toxicity included diarrhea 1 (3.7%), hypotension 2 (7.4%), nonneutropenic infection (11.1%), neutropenia 2 (7.4%), febrile neutropenia 2 (7.4%) (resulting in bendamustine dose reduction to 60 mg/m<sup>2</sup>), rash 1 (3.7%), fluid overload 2 (7.4%), and gastrointestinal bleeding 1 (3.7%). The most frequent grade 1-2 toxicities were constipation (26%) and fatigue (30%).

The data from this small retrospective study demonstrate excellent hematological responses. Impressively, 48% achieved VGPR or better (ITT). Sixty percent of patients treated with second-line BR achieved a VGPR. Furthermore, rituximab maintenance upgraded responses in the few patients that received this therapy.

Treatment in IgM-AL is not uniform, with poor responses to alkylators (responses 27% to 38%<sup>2,11,12</sup>) or purine-analog/anthracycline-containing therapy.<sup>1,2</sup> Outcomes with bortezomib-based therapy are mixed (VGPR or better of 27% and 42% in 2 studies).<sup>1,13</sup> A rituximab-bortezomib combination improved responses (ORR, 78%).<sup>3</sup> The high prevalence of disease-related neuropathy in IgM-AL provokes reticence in using bortezomib.

Furthermore, bortezomib is not funded in the United Kingdom for lymphoproliferative disorders. The few patients eligible for autologous stem cell transplantation appear to have good outcomes (ORR, 89% and 67% organ responses) but transplant-related mortality was 8%.<sup>4</sup> In a large European study, only 1.8% of patients were treated with autologous stem cell transplantation.<sup>1</sup> Disappointingly, the efficacy of ibrutinib in Waldenström macroglobulinemia (ORR, 91%)<sup>14</sup> was not replicated in AL.<sup>5</sup>

In conclusion, this study suggests that first-line BR leads to high response rates in IgM-AL. Bendamustine is not neurotoxic, dosing is not affected by renal impairment, and there is no known cardiac toxicity, rendering BR a widely applicable therapy in IgM-AL. Response appears durable, and maintenance rituximab may upgrade depth of response. The limitation of this study is one shared with almost all literature in IgM-AL given its rarity: it is small and retrospective. Larger collaborative studies are needed to confirm these results, and combination with novel proteasome inhibitors should be explored to further improve outcomes.

## Acknowledgments

The authors acknowledge their staff in echocardiography and histopathology and those involved in the clinical care of their patients. The alchemy study was performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, amended at the 52nd World Medical Association General Assembly, Edinburgh, Scotland, 2000. Informed written consent was obtained from the patients prior to registration into the study. The right of a patient to refuse participation without giving reasons is respected. Patients remain free to withdraw at any time from the study without giving reasons and without prejudicing his/her further treatment. Approval for this study was granted by the appropriate United Kingdom National Health Service Research Ethics Committee.

## Authorship

Contribution: R.M. and A.D.W. designed the study, collected and analyzed data, and wrote the paper; and S.S., S.M., D.F., F.S., T.L., C.Q., M.F., H.J.L., J.D.G., C.W., and P.N.H. managed patients and provided critical input prior to submission.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

Correspondence: Ashutosh Wechalekar, National Amyloidosis Centre, University College London (Royal Free Campus), Rowland Hill St, London NW3 2PF, United Kingdom; e-mail: a.wechalekar@ucl.ac.uk.

## REFERENCES

1. Sachchithanatham S, Roussel M, Palladini G, et al. European collaborative study defining clinical profile outcomes and novel prognostic criteria in monoclonal immunoglobulin m-related light chain amyloidosis. *J Clin Oncol*. 2016;34(17):2037-2045.
2. Terrier B, Jaccard A, Harousseau JL, et al. The clinical spectrum of IgM-related amyloidosis: a French nationwide retrospective study of 72 patients. *Medicine (Baltimore)*. 2008;87(2):99-109.
3. Palladini G, Foli A, Russo P, et al. Treatment of IgM-associated AL amyloidosis with the combination of rituximab, bortezomib, and dexamethasone. *Clin Lymphoma Myeloma Leuk*. 2011;11(1):143-145.
4. Valente M, Roy V, Lacy MQ, Dispenzieri A, Gertz MA. Autologous stem cell transplantation and IgM amyloidosis. *Leuk Lymphoma*. 2006;47(6):1006-1012.
5. Pika T, Hegenbart U, Flodrova P, Maier B, Kimmich C, Schönland SO. First report of ibrutinib in IgM-related amyloidosis: few responses, poor tolerability, and short survival. *Blood*. 2018;131(3):368-371.
6. Rummel MJ, Niederle N, Maschmeyer G, et al; Study group indolent Lymphomas (StiL). Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. *Lancet*. 2013;381(9873):1203-1210.
7. Treon SP, Hanzis C, Tripsas C, et al. Bendamustine therapy in patients with relapsed or refractory Waldenström's macroglobulinemia. *Clin Lymphoma Myeloma Leuk*. 2011;11(1):133-135.
8. Milani P, Schonland S, Palladini G, et al. Response to bendamustine is associated with a survival advantage in heavily pretreated patients with AL amyloidosis. *Amyloid*. 2017;24(suppl 1):56-57.
9. Gertz MA, Comenzo R, Falk RH, et al. Definition of organ involvement and treatment response in immunoglobulin light chain amyloidosis (AL): a consensus opinion from the 10th International Symposium on Amyloid and Amyloidosis. *Am J Hematol*. 2005;79(4):319-328.
10. Comenzo RL, Reece D, Palladini G, et al. Consensus guidelines for the conduct and reporting of clinical trials in systemic light-chain amyloidosis. *Leukemia*. 2012;26(11):2317-2325.
11. Wechalekar AD, Lachmann HJ, Goodman HJ, Bradwell A, Hawkins PN, Gillmore JD. AL amyloidosis associated with IgM paraproteinemia: clinical profile and treatment outcome. *Blood*. 2008;112(10):4009-4016.
12. Palladini G, Russo P, Bosoni T, et al. AL amyloidosis associated with IgM monoclonal protein: a distinct clinical entity. *Clin Lymphoma Myeloma*. 2009;9(1):80-83.
13. Sissoko M, Sancharowala V, Seldin D, et al. Clinical presentation and treatment responses in IgM-related AL amyloidosis. *Amyloid*. 2015;22(4):229-235.
14. Treon SP, Tripsas CK, Meid K, et al. Ibrutinib in previously treated Waldenström's macroglobulinemia. *N Engl J Med*. 2015;372(15):1430-1440.

DOI 10.1182/blood-2018-04-846493

© 2018 by The American Society of Hematology