RESEARCH LETTER

blood advances

TO THE EDITOR:

Ibrutinib or non-BTK inhibitor therapy in relapsed Waldenström macroglobulinemia: a real-life multicenter Italian study

Francesco Autore,[1] Alessandra Tedeschi,[2] Giulia Benevolo,[3] Nicolò Danesin,[4] Diana Giannarelli,[1] Rita Rizzi,[5] Emanuele Cencini,[6] Veronica Mattiello,[7] Isacco Ferrarini,[8] Raffaella Pasquale,[9] Ilaria Del Giudice,[10] Angela Ferrari,[11] Martina Bullo,[12] Bernardo Rossini,[13] Marina Motta,[14] Dario Marino,[15] Idanna Innocenti,[1] Luca Stirparo,[1] Diego Petrilli,[1] Pellegrino Musto,[5] Veronica Peri,[3] Giulia Zamprogna,[2] Stefan Hohaus,[1,16] Anna Maria Frustaci,[2] Francesco Piazza,[4] Simone Ferrero,[3] and Luca Laurenti[1,16]

[1]Department of Laboratory and Hematological Sciences, Fondazione Policlinico Gemelli IRCCS, Rome, Italy; [2]Niguarda Cancer Center, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; [3]Ematologia Universitaria A.O.U. Città della Salute e della Scienza di Torino, Turin, Italy; [4]Hematology Unit, Department of Medicine, University of Padova, Padua, Italy; [5]Dipartimento di Medicina di Precisione e Rigenerativa e Area Ionica (DIMEPRE-J), Scuola di Medicina, Universita' degli Studi "Aldo Moro," e SC di Ematologia con Trapianto, AOU Consorziale Policlinico, Bari, Italy; [6]A.O.U. Senese and University of Siena, Siena, Italy; [7]Hematology Unit, Fondazione IRCCS Ca' Grande Ospedale Maggiore Policlinico, Milan, Italy; [8]Hematology Unit, Section of Biomedicine of Innovation, Department of Engineering for Innovation Medicine, University of Verona, Verona, Italy; [9]SOC Clinica Ematologica–Centro Trapianti e Terapie Cellulari, Azienda Sanitaria Universitaria Friuli Centrale, Udine, Italy; [10]Ematologia, Dipartimento di Medicina Traslazionale e di Precisione, Sapienza Università di Roma, AOU Policlinico Umberto I, Rome, Italy; [11]Arcispedale Santa Maria Nuova IRCCS, Reggio Emilia, Italy; [12]A.O. Ordine Mauriziano di Torino, Turin, Italy; [13]IRCCS Istituto Tumori "Giovanni Paolo II," Bari, Italy; [14]ASST Spedali Civili Brescia, Brescia, Italy; [15]Istituto Oncologico Veneto IOV-IRCCS, Padua, Italy; and [16]Section of Hematology, Department of Radiological and Hematological Sciences, Catholic University, Rome, Italy

In Waldenström macroglobulinemia (WM), the treatment scenario includes a wide range of approaches, including monoclonal antibodies, alkylating agents, proteasome inhibitors, and Bruton tyrosine kinase inhibitors (BTKi). Although long progression-free survival (PFS) is common after first-line therapy, most patients eventually require second-line therapy.[1-3]

Symptomatic patients with relapsed WM treated with standard rituximab plus chemotherapy generally show an 18-month PFS of ~50%.[4,5] Paludo et al described 44 previously treated patients receiving BR (bendamustine-rituximab), who achieved an overall response rate (ORR) of 95% and a median PFS of 58 months, showing superior efficacy compared with DRC (dexamethasone-rituximab-cyclophosphamide).[6] Rituximab-based combinations, such as BR or rituximab plus bortezomib, have also demonstrated good activity with acceptable toxicity, mainly neutropenia for BR and neuropathy for bortezomib.[7-10] BTKi have recently become standard in relapsed WM, with PFS rates of 69.7% for ibrutinib and 78.3% for zanubrutinib at 42 months[11] and 52% for acalabrutinib at 63 months.[12] However, in the setting of patients with relapsed WM, chemotherapy and/or immunotherapy (CIT; non-BTKi therapy) has been substantially substituted by BTKi. Previous trials have investigated the efficacy and safety of BTKi in second-line without a direct comparison to non-BTKi therapy.[13-15]

We conducted a retrospective, multicenter analysis comparing BTKi with CIT as second-line therapy in relapsed WM. The primary end points were ORR, which reflect the best overall response achieved in the treatment, PFS, and overall survival (OS), assessed according to the simplified 6th International Workshop on WM response criteria, which use immunoglobulin M levels alone to categorize responses as very good partial response or less.[16] All patients provided informed consent and the study was conducted per the Declaration of Helsinki.

Our data set consisted of all patients with WM consecutively diagnosed with relapsed WM and treated between 2008 and 2022 in 15 clinical centers affiliated to the Fondazione Italiana Linfomi. Patients were retrospectively identified through institutional databases, and the choice of treatment was at the discretion of the treating physician, according to patient comorbidities, and clinical practice at the time. The statistical analyses were conducted on 2 different treatment groups: ibrutinib (zanubrutinib not

Submitted 13 June 2025; accepted 22 January 2026; prepublished online on *Blood Advances* First Edition 12 February 2026; final version published online 16 April 2026. https://doi.org/10.1182/bloodadvances.2025017464.

Deidentified individual participant data that underlie the reported results and data sets used and/or analyzed during this study are available from the corresponding author, Francesco Autore (francesco.autore@policlinicogemelli.it), on reasonable request.

The full-text version of this article contains a data supplement.

Table 1. Patient characteristics of the ibrutinib arm and non-BTKi arm

	Ibrutinib (85 patients)	Non-BTKi treatments (BR + DRC + bortezomib-based) (70 patients)	*P* value
Age at treatment, median (Q1-Q3), y	75 (64-81)	72 (64-79)	.213
Sex, n (%)			.566
M	56 (65.9)	43 (61.4)	
F	29 (34.1)	27 (38.6)	
Hb, median (Q1-Q3), g/dL	10.10 (9.40-11.53)	10.50 (9.35-11.85)	.601
Platelets, median (Q1-Q3), $\times 10^9$/L	210.5 (152.5-305.8)	214.0 (156.0-261.0)	.45
Prot tot, median (Q1-Q3), g/dL	8.0 (7.2-8.9)	8.1 (7.2-9.7)	.378
IgM, median (Q1-Q3), mg/L	2030 (525-3863)	2835 (1868-4251)	.024
IPSSWM, n (%)			.719
1	18 (23.4)	18 (28.1)	
2	37 (48.0)	31 (48.4)	
3	22 (28.6)	15 (23.4)	
NA	8	9	
MYD88mut, n (%)			.695
Negative	6 (10.5)	5 (13.2)	
Positive	51 (89.5)	33 (86.8)	
NA	28	32	
CXCR4mut, n (%)			.116
Negative	20 (87.0)	7 (63.6)	
Positive	3 (13.0)	4 (36.4)	
NA	62	73	
CrCl, median (Q1-Q3), mL/min	67.50 (52.25-80.00)	68.00 (57.50-90.00)	.321
CrCl <70 mL/min, n (%)			.677
No	37 (45.1)	33 (48.5)	
Yes	45 (54.9)	35 (51.5)	
NA	3	2	
CrCl <50 mL/min			.057
No	64 (78.0)	61 (89.7)	
Yes	18 (22.0)	7 (10.3)	
NA	3	6	
CIRS >6, n (%)			.683
No	60 (73.2)	47 (70.1)	
Yes	22 (26.8)	20 (29.9)	
NA	3	3	
Cardiac comorbidity, n (%)			.726
No	79 (92.9)	64 (91.4)	
Yes	6 (7.1)	6 (8.6)	
Respiratory comorbidity, n (%)			.678
No	83 (97.7)	69 (98.6)	
Yes	2 (2.3)	1 (1.4)	

CIRS, cumulative illness raring scale; CrCl, creatinine clearance; DRC, dexamethasone-rituximab-cyclophosphamide; F, female; Hb, hemoglobin; IgM, immunoglobulin M; IPSSWM, International Prognostic Scoring System for Waldenstrom Macroglobulinemia; M, male; NA, not available; Prot tot, total proteins.

available at that time) vs non-BTKi (BR, DRC, and bortezomib-based regimens). PFS, time to next treatment (TTNT), and OS were defined as the time from initiation of second-line treatment to a new progression of the disease, death, or end of follow-up; to first date of third-line treatment, death, or end of follow-up; and to death or censored at the end of follow-up, respectively.

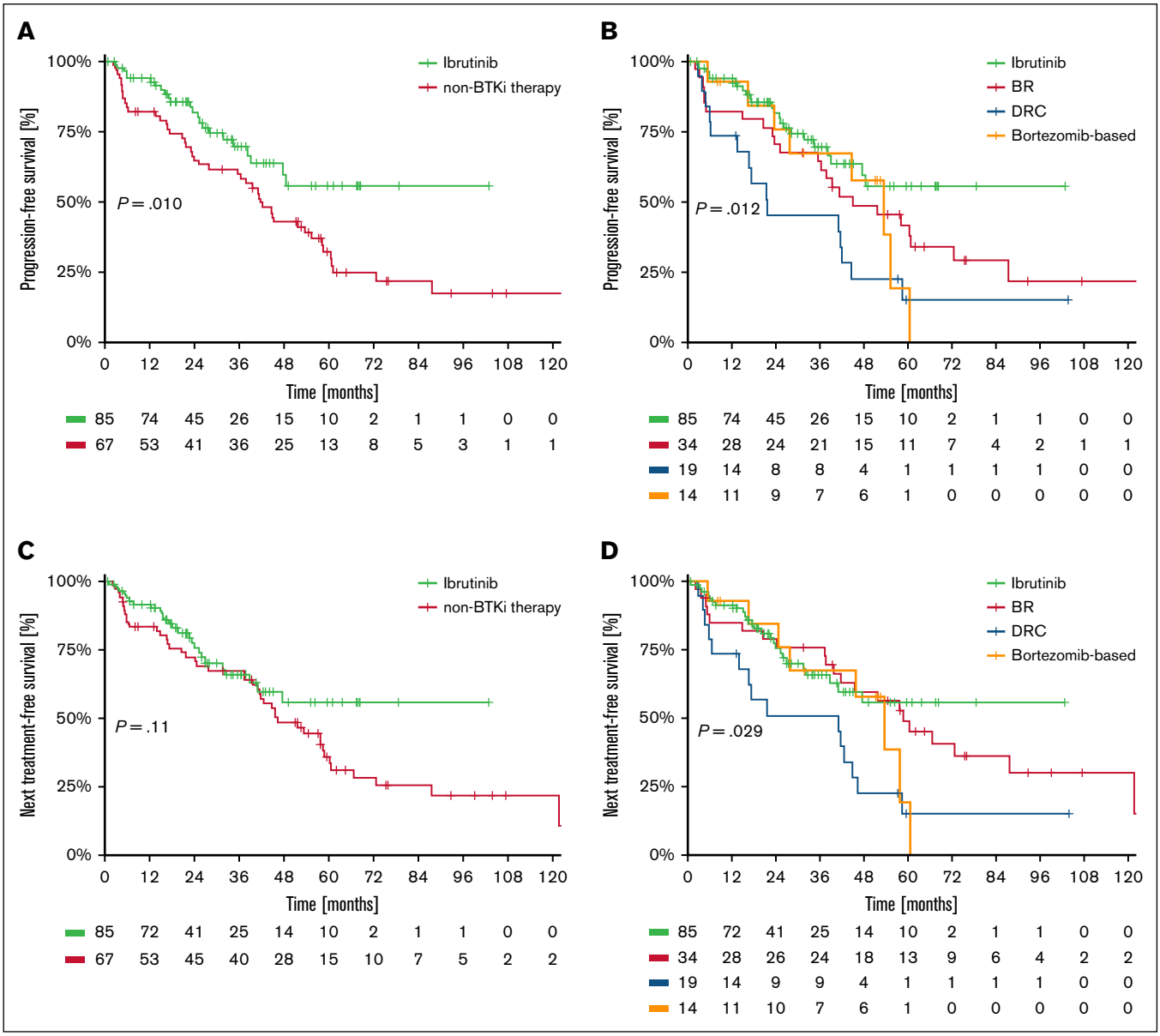

Figure 1. Outcomes of ibrutinib vs non-BTKi therapy patients. (A) PFS of ibrutinib compared with non-BTKi therapy. (B) PFS of ibrutinib compared with the 3 curves of the different non-BTKi therapy. (C) TTNT of ibrutinib compared with non-BTKi therapy. (D) TTNT of ibrutinib compared with the 3 curves of the different non-BTKi therapy.

For outcomes analysis, patients who received as second-line therapy the same chemotherapy received as first-line were excluded from analysis (2 patients for DRC and 1 for bortezomib).

We included 155 patients with relapsed WM: 85 treated with ibrutinib and 70 with non-BTKi therapy (34 BR, 21 DRC, and 15 bortezomib-based regimens). Patient characteristics are summarized in Table 1 and supplemental Table 1. The 2 cohorts, ibrutinib and non-BTKi therapy, showed similar baseline clinical characteristics, prognostic factors including mutational status of *MYD88* and *CXCR4*, comorbidities, and interval times of retreatment between first- and second-line treatment (34 vs 30 months; $P = .83$). Median follow-up was 48 months (quartile 1 [Q1]-Q3, 26-72) for the entire cohort, 34 months for ibrutinib, and 75 months for non-BTKi therapy. The median number of cycles administered was 6 for BR, 6 for DRC, and 6 for bortezomib-based therapy. Treatment modifications were reported in 34.1% of ibrutinib vs 31.4% of non-BTKi therapy patients ($P = .72$). Dose reductions occurred in 17.6% vs 11.4%, respectively ($P = .28$). In the non-BTKi therapy group, 25.7% had a cycle reduction. Treatment modifications occurred in 11 of 34 BR patients (32.4%; 7 cycle reduction, 2 dose reduction, and 2 both), 9 of 21 DRC patients (42.9%; 6 cycle reduction, 1 dose reduction, and 2 both), and 2/15 bortezomib-based patients (13.3%; 1 cycle reduction and 1 dose reduction). In the ibrutinib group, dose reductions occurred in 17.6%, temporary interruptions occurred in 10.6%,

and permanent discontinuation in 22.4%. The main reason for treatment modifications was nonhematologic toxicity (79.3% in the ibrutinib group and 50% in the CIT group).

ORR was 84.7% in the ibrutinib group vs 74.6% in non-BTKi therapy ($P = .12$). In the ibrutinib group median duration of response was not yet reached; at 4 years, 68% of responding patients were still in response, whereas in the non-BTKi group, the corresponding value at 4 years was 50%, and the median duration of response was 45.0 months (95% confidence interval, 29.6-60.5; $P < .001$). Four-year PFS was significantly longer with ibrutinib (59.7% vs 42.9%; $P = .010$; Figure 1A), with a median PFS not reached for ibrutinib and 41.6 months (95% confidence interval, 34.3-48.9) for non-BTK therapy. Four-year TTNT was 55.8% vs 48.4% ($P = .11$; Figure 1C), and 4-year OS was 78% in both groups ($P = .64$). ORR did not differ, independently from treatment modifications or toxicities. Among non-BTKi therapy subgroups, median ages were similar (BR, 70 years; DRC, 75 years; bortezomib-based, 68 years; $P = .37$). BR showed a median PFS of 45.0 months, bortezomib-based 53.6 months, and DRC 21.7 months. Ibrutinib showed superior outcomes compared with all non-BTKi therapy regimens combined, both in term of PFS ($P = .012$) and TTNT ($P = .029$; Figure 1B,D). When comparing ibrutinib to each of the 3 non-BTKi therapy groups, different ORRs were observed in each group with ibrutinib reporting a rate of 84.7% (vs 76.5% for BR, 63.2% for DRC, and 85.7% for bortezomib). Four-year PFS of ibrutinib (59.7%) was significantly superior to 4-year PFS of DRC (22.7%; $P < .001$) but not to that of BR (48.8%; $P = .11$) and of bortezomib based (57.9%; $P = .21$). For TTNT and OS, differences were generally nonsignificant, except for ibrutinib vs DRC (OS, $P = .039$; TTNT, $P = .004$). No differences were noted in the 2 subgroups of ibrutinib patients who were treated with BR or DRC as first-line therapy in terms of PFS, TTNT, OS, ORR, and withdrawal or dose reduction due to toxicity.

In the end excluding 11 MYD88 wild-type patients, the ORR was 84.8% in the ibrutinib group vs 72.6% in non-BTKi therapy ($P = .075$). The 4-year PFS was significantly longer with ibrutinib (58.8% vs 41.1%; $P = .011$), no differences were observed for TTNT and OS.

Multivariable analysis found choice of the treatment of non-BTKi therapy vs ibrutinib hazard ratio (HR; HR, 2.77) and increased β2-microglobulin (HR, 1.20) as significant variables that unfavorably impact on PFS; choice of the treatment of non-BTKi therapy vs ibrutinib (HR, 1.87), older age (HR = 1.06), and male gender (HR, 2.57) on TTNT; and older age (HR, 1.12) and male sex (HR, 1.91) on OS.

This retrospective real-life study showed advantages of ibrutinib vs non-BTKi therapy in terms of PFS and TTNT, but not in terms of OS, except for DRC group, for which the ibrutinib advantage was statistically significant.

Our study highlights that ibrutinib achieves a higher ORR (84.7%) and significantly superior 4-year PFS (59.7%) compared to non-BTKi therapy overall (42.9%, $P = .010$), with the most pronounced benefit seen over DRC. Ibrutinib and BR were comparable, largely driven by the inferior outcome of patients who were administered DRC in non-BTKi group. No significant OS differences were observed, except for a modest advantage of ibrutinib over DRC. Although follow-up differed between cohorts, with longer observation in the non-BTKi group, the 4-year outcomes align with the median follow-up of the entire series, allowing a robust comparison.

Overall, our findings support the growing role of BTKi as a preferred option in the relapsed setting, although BR remains a competitive alternative considering the sequencing and the limited other agents available. This study, despite limitations related to its retrospective design and small sample size, reinforces the need for individualized treatment strategies in relapsed/refractory WM.

Acknowledgments: The authors thank the Fondazione Italiana Linfomi for contribution of patient data.

The authors acknowledge support from the Ministry of Health (Ricerca Corrente 2025).

Contribution: F.A., A.T., S.F., and L.L. performed research; G.B., N.D., R.R., E.C., V.M., I.F., R.P., I.D.G., A.F., M.B., B.R., M.M., D.M., I.I., L.S., D.P., P.M., V.P., G.Z., S.H., A.M.F., and F.P. collected data; D.G. performed data analysis; F.A., D.G., and L.L. wrote the manuscript; A.T., F.P., and S.F. supervised the study; and all authors reviewed the manuscript.

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

ORCID profiles: F.A., 0000-0002-7868-7469; G.B., 0000-0002-3200-9654; N.D., 0009-0004-1352-306X; R.R., 0000-0002-2557-1235; I.F., 0000-0001-9867-8335; R.P., 0000-0003-2253-8883; B.R., 0000-0003-2348-5437; P.M., 0000-0003-3277-6594; S.H., 0000-0002-5534-7197; A.M.F., 0000-0003-2587-7901; F.P., 0000-0002-2831-623X; S.F., 0000-0002-9711-1502; L.L., 0000-0002-8327-1396.

Correspondence: Francesco Autore, Fondazione Policlinico Universitario A. Gemelli IRCCS, Largo Agostino Gemelli 8, I-00168 Rome, Italy; email: francesco.autore@policlinicogemelli.it.

References

1. Buske C, Castillo JJ, Abeykoon JP, et al. Report of consensus panel 1 from the 11th International Workshop on Waldenstrom's Macroglobulinemia on management of symptomatic, treatment-naïve patients. *Semin Hematol*. 2023;60(2):73-79.
2. Buske C, Seymour JF. Immunochemotherapy in Waldenström macroglobulinemia – still the backbone of treatment. *Leuk Lymphoma*. 2015;56(9):2489-2490.
3. D'Sa S, Matous JV, Advani R, et al. Report of consensus panel 2 from the 11th international workshop on Waldenström's macroglobulinemia on the management of relapsed or refractory WM patients. *Semin Hematol*. 2023;60(2):80-89.
4. Tedeschi A, Benevolo G, Varettoni M, et al. Fludarabine plus cyclophosphamide and rituximab in Waldenstrom macroglobulinemia. *Cancer*. 2012;118(2):434-443.
5. Buske C, Tedeschi A, Trotman J, et al. Ibrutinib plus rituximab versus placebo plus rituximab for Waldenström's macroglobulinemia: final analysis from the randomized phase III iNNOVATE study. *J Clin Oncol*. 2022;40(1):52-62.

6. Paludo J, Abeykoon JP, Shreders A, et al. Bendamustine and rituximab (BR) versus dexamethasone, rituximab, and cyclophosphamide (DRC) in patients with Waldenstrom macroglobulinemia. *Ann Hematol*. 2018;97(8):1417-1425.

7. Ghobrial IM, Hong F, Padmanabhan S, et al. Phase II trial of weekly bortezomib in combination with rituximab in relapsed or relapsed and refractory Waldenstrom macroglobulinemia. *J Clin Oncol*. 2010; 28(8):1422-1428.

8. Tedeschi A, Picardi P, Ferrero S, et al. Bendamustine and rituximab combination is safe and effective as salvage regimen in Waldenström macroglobulinemia. *Leuk Lymphoma*. 2015;56(9):2637-2642.

9. Benevolo G, Drandi D, Villivà N, et al. Efficacy and safety of bendamustine, rituximab and bortezomib treatment in relapsed/ refractory Waldenstrom Macroglobulinaemia: results of phase 2 single-arm FIL-BRB trial. *Br J Haematol*. 2025;206(2):556-564.

10. Pratt G, El-Sharkawi D, Kothari J, et al. Diagnosis and management of Waldenstrom macroglobulinaemia-a British Society for Haematology guideline. *Br J Haematol*. 2022;197(2):171-187.

11. Dimopoulos MA, Opat S, D'Sa S, et al. Zanubrutinib versus ibrutinib in symptomatic Waldenström macroglobulinemia: final analysis from the randomized phase III ASPEN study. *J Clin Oncol*. 2023;41(33): 5099-5106.

12. Owen R, McCarthy H, Rule S, et al. P1130: Acalabrutinib in treatment-naive or relapsed/refractory Waldenström macroglobulinemia: 5-year follow-up of a phase 2, single-arm study. *HemaSphere*. June 2022;6:1020-1021.

13. Dimopoulos MA, Trotman J, Tedeschi A, et al; iNNOVATE Study Group and the European Consortium for Waldenström's Macroglobulinemia. Ibrutinib for patients with rituximab-refractory Waldenström's macroglobulinaemia (iNNOVATE): an open-label substudy of an international, multicentre, phase 3 trial. *Lancet Oncol*. 2017;18(2):241-250.

14. Trotman J, Buske C, Tedeschi A, et al. Single-agent ibrutinib for rituximab-refractory Waldenström macroglobulinemia: final analysis of the substudy of the phase III InnovateTM trial. *Clin Cancer Res*. 2021; 27(21):5793-5800.

15. Yi S, Cai Z, Hu Y, et al. Ibrutinib efficacy, safety, and pharmacokinetics in Chinese patients with relapsed or refractory Waldenström's macroglobulinemia: a multicenter, single-arm, phase 4 study. *Adv Ther*. 2024;41(2):672-685.

16. Treon SP, Tedeschi A, San-Miguel J, et al. Report of consensus panel 4 from the 11th International Workshop on Waldenstrom's Macroglobulinemia on diagnostic and response criteria. *Semin Hematol*. 2023;60(2):97-106.