



# A single-center retrospective study suggests a potential benefit of BTK inhibitor-based therapy in patients with histologic transformation of Waldenström macroglobulinemia

Yi Xia, Haorui Shen , Yi Miao, Yuxiao Zhao , Hailing Liu, Sanmei Wang , Tian Tian , Ji Xu , Xiaoyan Qu , Jianyong Li & Lei Fan

To cite this article: Yi Xia, Haorui Shen , Yi Miao, Yuxiao Zhao , Hailing Liu, Sanmei Wang , Tian Tian , Ji Xu , Xiaoyan Qu , Jianyong Li & Lei Fan (2026) A single-center retrospective study suggests a potential benefit of BTK inhibitor-based therapy in patients with histologic transformation of Waldenström macroglobulinemia, *Annals of Medicine*, 58:1, 2624909, DOI: [10.1080/07853890.2026.2624909](https://doi.org/10.1080/07853890.2026.2624909)

To link to this article: <https://doi.org/10.1080/07853890.2026.2624909>



© 2026 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group



[View supplementary material](#)



Published online: 09 Mar 2026.



[Submit your article to this journal](#)



Article views: 632








[View related articles](#)



[View Crossmark data](#)

# A single-center retrospective study suggests a potential benefit of BTK inhibitor-based therapy in patients with histologic transformation of Waldenström macroglobulinemia

Yi Xia<sup>a,b,c#</sup> , Haorui Shen<sup>a,b,c#</sup>, Yi Miao<sup>a,b,c#</sup> , Yuxiao Zhao<sup>a,b,c</sup>, Hailing Liu<sup>a,b,c</sup> ,  
Sanmei Wang<sup>a,b,c</sup>, Tian Tian<sup>a,b,c</sup>, Ji Xu<sup>a,b,c</sup>, Xiaoyan Qu<sup>a,b,c</sup>, Jianyong Li<sup>a,b,c,d</sup>  and Lei Fan<sup>a,b,c</sup> 

<sup>a</sup>Department of Hematology, the First Affiliated Hospital with Nanjing Medical University, Jiangsu Province Hospital, Nanjing, China; <sup>b</sup>Key Laboratory of Hematology of Nanjing Medical University, Nanjing, China; <sup>c</sup>Collaborative Innovation Center for Cancer Personalized Medicine, Nanjing, China; <sup>d</sup>National Clinical Research Center for Hematologic Diseases, The First Affiliated Hospital of Soochow University, Suzhou, China

## ABSTRACT

**Background:** Histologic transformation from Waldenström macroglobulinemia (WM) to diffuse large B-cell lymphoma (DLBCL) is a rare but clinically challenging event.

**Methods:** In this retrospective study, we analyzed 15 cases of histologic transformation among WM patients treated at the Department of Hematology, Jiangsu Province Hospital, between October 2015 and February 2025.

**Results:** The median age at transformation was 67 years, with a median time from initial WM diagnosis to transformation of 8 months (range: 0–177 months). Six patients (40%) received no WM-directed therapy before transformation. At transformation, 13 patients (86.7%) had stage IV disease. Extranodal involvement was frequent: 6 patients (40%) had  $\geq 2$  extranodal sites involved, with the most common sites being bone/bone marrow (each 33.3%), central nervous system (CNS, 20.0%), and nasopharynx/testis/gastrointestinal tract/peritoneum/skin (each 13.3%). Involvement of immune-privileged sites (CNS, testis) was observed in 5 patients (33.3%). Immunophenotyping revealed 13 cases (86.7%) as non-germinal center B-cell (non-GCB) DLBCL. Prognostic analysis showed a median overall survival (OS) of 26.0 months from transformation. Patients receiving Bruton's tyrosine kinase inhibitor (BTKi)-based regimens after transformation showed significantly prolonged OS ( $p=0.007$ ). Additionally, patients receiving BTKi-based therapy at any point showed a trend toward improved survival ( $p=0.092$ ).

**Conclusions:** Although rare, histologic transformation from WM to DLBCL exhibits aggressive clinical behavior, frequent extranodal involvement, and poor prognosis. BTKi-based regimens may provide significant survival benefits in this patient population.

## KEY MESSAGES

- This first report characterizes the clinicopathological features of Asian patients with transformed WM, which align with Western observations.
- In this cohort, we first reported BTKi-based regimens may improve treatment responses and survival, supporting their therapeutic potential.

## ARTICLE HISTORY

Received 19 October 2025





Accepted 27 January 2026

## KEYWORDS


Waldenström macroglobulinemia; diffuse large B-cell lymphoma; histologic transformation; BTK inhibitor

## Introduction

Waldenström macroglobulinemia (WM) is a rare indolent B-cell lymphoma characterized by bone marrow lymphoplasmacytic infiltration and monoclonal IgM protein production [1,2]. Although WM typically follows an indolent clinical course, approximately 2–10% of patients experience histologic transformation to aggressive lymphoma, most commonly diffuse large B-cell lymphoma (DLBCL) [3–6]. A long-term follow-up study by Castillo et al. reported cumulative incidences of DLBCL transformation at 5, 10, and 15 years as 1.0%, 2.4%, and 3.8%, respectively [3].

**CONTACT** Lei Fan  [fanlei@jsph.org.cn](mailto:fanlei@jsph.org.cn)  Department of Hematology, the First Affiliated Hospital with Nanjing Medical University, Jiangsu Province Hospital, Nanjing, China; Jianyong Li  [lijianyonglm@126.com](mailto:lijianyonglm@126.com)  Department of Hematology, the First Affiliated Hospital with Nanjing Medical University, Jiangsu Province Hospital, Nanjing, China.

<sup>#</sup>These authors contributed equally to this work.

 Supplemental data for this article can be accessed online at <https://doi.org/10.1080/07853890.2026.2624909>.

© 2026 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited. The terms on which this article has been published allow the posting of the Accepted Manuscript in a repository by the author(s) or with their consent.

WM-to-DLBCL transformation can occur at any stage of the disease, including at initial diagnosis, before treatment, during therapy, or after treatment completion, and shows highly heterogeneous clinicopathological features. Compared to non-transformed WM patients, those with transformed WM (tWM) have significantly worse prognoses, frequent extranodal involvement. Central nervous system (CNS) involvement is particularly notable, occurring in 13–18% of cases [7].

Ibrutinib, the first BTKi, was approved by the National Medical Products Administration of China in November 2018 for relapsed or refractory WM and was later for first-line use. Since then, WM's therapeutic landscape has changed significantly. However, no systematic studies have characterized the epidemiologic and clinical outcomes of Chinese patients with tWM or assessed BTKi-based treatment impact in this population. Therefore, this retrospective study describes the clinicopathological features and outcomes of patients with biopsy-confirmed tWM at our center to provide evidence-based insights to inform clinical decision-making.

## Materials and methods

We retrospectively analyzed patients treated at the Department of Hematology, Jiangsu Province Hospital between October 2015 and February 2025. We included patients with confirmed WM who were subsequently diagnosed with aggressive lymphoma, either concurrently or later. Pathologic diagnosis was established through independent review by two senior hematopathologists.

Treatment response in WM was evaluated based on the updated response criteria from the 11th International Workshop on Waldenström's Macroglobulinemia (IWWM-11) [8], while response in DLBCL was assessed according to the Lugano 2014 criteria [9]. Immunohistochemical classification of DLBCL into germinal center B-cell-like (GCB) or non-germinal center B-cell-like (non-GCB) subtypes was performed using the Hans algorithm. This study was approved by the Ethics Committee of Jiangsu Province Hospital (No. 2025-SR-435) and was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent.

The time from WM diagnosis to histologic transformation was defined as the interval between the initial WM diagnosis and the pathological confirmation of transformation. Post-transformation overall survival (OS) was defined as the interval from the date of histologic transformation to either the last follow-up or death. OS from WM diagnosis was defined as the interval from the initial diagnosis of WM to the last follow-up or death. Survival curves were generated using the Kaplan–Meier method, and comparisons between groups were performed using the log-rank test. All statistical analyses were conducted using SPSS software (version 25.0) and GraphPad Prism (version 9.0). All tests were two-sided, and a  $p$  value of  $<0.05$  was considered statistically significant.

## Results

A total of 15 patients with histologic transformation from WM to aggressive lymphoma were included in this study; all cases transformed into DLBCL. The clinical characteristics of the patients at the time of WM diagnosis are summarized in Table 1.

The median age at WM diagnosis was 64 years. *MYD88*<sup>L265P</sup> and *CXCR4* mutations were detected in 90% and 30% of patients, respectively, with 40% classified as high-risk by the International Prognostic Scoring System for WM (IPSSWM). The median time from WM diagnosis to histologic transformation was 8 months (range: 0–177 months).

Among the 15 patients, 4 had simultaneous WM and DLBCL diagnoses, while 11 were initially diagnosed with WM before developing DLBCL. Of these 11 patients, 2 received no prior treatment, 3 were in treatment-free intervals, and 6 transformed during WM-directed therapy. Notably, three patients transformed while receiving BTKi therapy after 19, 4, and 9 months of treatment, respectively.

The clinical and pathological characteristics of DLBCL following histologic transformation from WM are summarized in Table 2. The median age at DLBCL diagnosis was 67 years, with 86.7% (13/15) of patients being aged  $\geq 60$  years. At transformation, 86.7% (13/15) of patients had stage IV disease. B symptoms were observed in 73.3% (11/15), and elevated lactate dehydrogenase (LDH) levels were found in 50% (7/14) of patients with available data. High-intermediate or high-risk International Prognostic Index (IPI)

**Table 1.** Baseline clinical and molecular characteristics of patients with WM.

Clinical characteristic	Number (%)
Sex	
Male	9 (60%)
Female	6 (40%)
Age at WM diagnosis	Median 64 years (range: 45–77)
<60 years	4 (26.7%)
≥60 years	11 (73.3%)
Serum IgM level (g/L)	Median 23.4 (range: 7.2–64.7)
Mutations	
MYD88 <sup>L265P</sup> (n = 10)	9 (90%)
CXCR4 (n = 10)	3 (30%)
TP53 (n = 10)	4 (40%)
IPSSWM risk group	
Low	4 (26.7%)
Intermediate	5 (33.3%)
High	6 (40%)
WM treatment prior to transformation (n = 11) <sup>a</sup>	
Untreated	2 (18.2%)
Rituximab-based regimens	7 (63.6%)
BTK inhibitors	3 (27.3%)
Alkylating agents	6 (54.5%)
Purine analogs	3 (27.3%)

BTKi, Bruton's tyrosine kinase inhibitor; IPSSWM, International Prognostic Scoring System for Waldenström Macroglobulinemia; WM, Waldenström macroglobulinemia.

<sup>a</sup>Excluding 4 patients who were diagnosed with DLBCL concurrently with WM.

**Table 2.** Clinical and pathological characteristics of DLBCL following histologic transformation from WM.

Characteristic	Number (%)
Age at DLBCL diagnosis	Median 67 years (range: 49–87)
<60 years	2 (13.3%)
≥60 years	13 (86.7%)
DLBCL stage	
Primary CNS lymphoma	1 (6.7%)
Stage I	1 (6.7%)
Stage IV	13 (86.6%)
B symptoms	11 (73.3%)
Elevated LDH	7/14 (50.0%)
LDH level (U/L)	Median 285 (range: 131–1018)
IgM level at DLBCL diagnosis (g/L)	Median 13.3 (range: 5.7–49.2)
International prognostic index (IPI)	
Low risk	0
Low-intermediate risk	1 (6.7%)
High-intermediate risk	5 (33.3%)
High risk	9 (60.0%)
Extranodal involvement ≥2 sites	6 (40.0%)
Involvement of immune-privileged sites	5 (33.3%)
Hans classification	
GCB subtype	2 (13.3%)
Non-GCB subtype	13 (86.7%)
Double-expressor DLBCL (n = 12)	7 (58.3%)

DLBCL, diffuse large B-cell lymphoma; IPI, International Prognostic Index; GCB, germinal center B-cell-like; non-GCB, non-germinal center B-cell-like; LDH, lactate dehydrogenase; CNS, central nervous system; WM, Waldenström macroglobulinemia.

scores were observed in 93.3% (14/15) of patients. Extranodal involvement at ≥2 sites occurred in 40% (6/15) of patients, and 33.3% (5/15) had immune-privileged site involvement. Among the latter, the CNS was affected in three patients (all with multiple parenchymal lesions) and the testis in two. Other involved extranodal sites included bone (33.3%, 5/15), bone marrow (33.3%, 5/15), nasopharynx (13.3%, 2/15), gastrointestinal tract (13.3%, 2/15), pleuroperitoneum (13.3%, 2/15), skin (13.3%, 2/15), liver (6.7%, 1/15), and orbit (6.7%, 1/15).

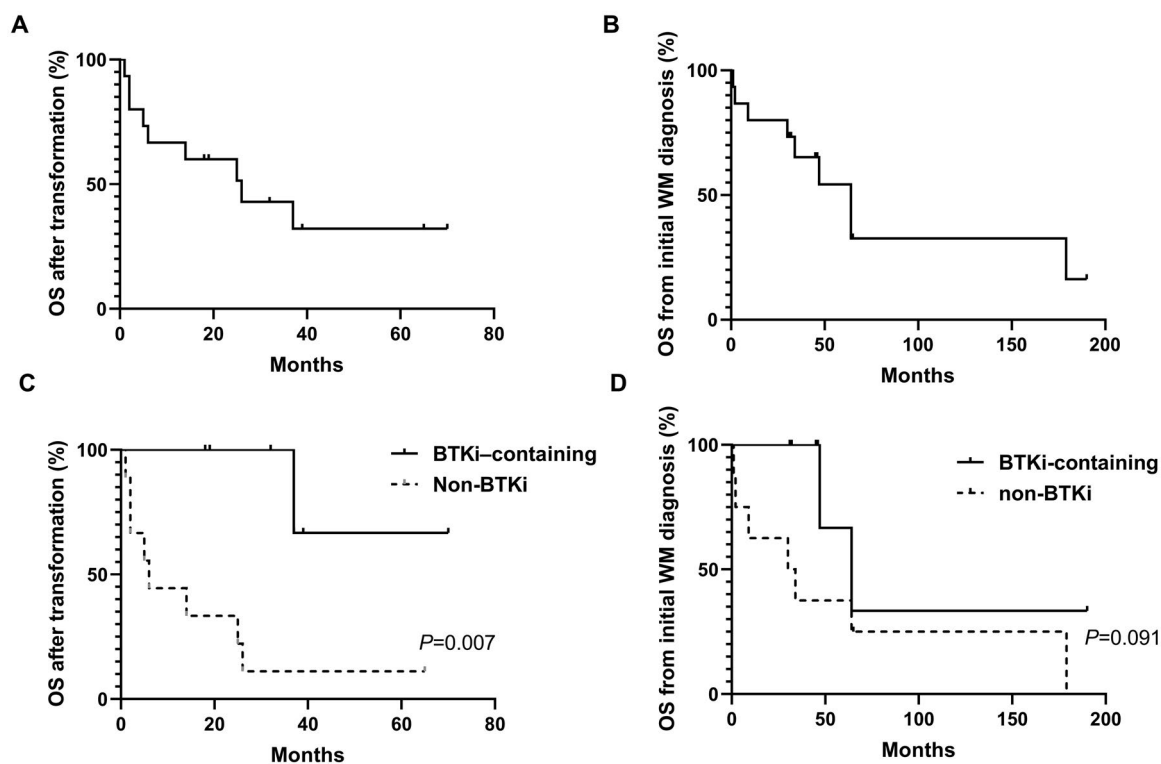
Immunohistochemical profiling showed CD10 positivity in 13.3% (2/15), BCL6 positivity in 53.3% (8/15), and MUM1 positivity in 93.3% (14/15) of DLBCL cases. Among evaluable cases, BCL2 positivity was detected in 92.3% (12/13), and c-Myc positivity in 66.7% (8/12). The median Ki-67 proliferation index was 85% (range: 60%–90%, n = 13). All tested cases (13/13) were negative for Epstein–Barr virus-encoded RNA (EBER) by *in situ* hybridization. Among six evaluable cases, five (83.3%) showed consistent light chain restriction between WM and DLBCL components, suggesting clonal relationship.

**Table 3.** First-line treatment regimens and responses following histologic transformation from WM to DLBCL.

First-line treatment after transformation	Number (%)	Response outcome
R-CHOP	7 (46.7%)	1 CR, 2 PR <sup>a</sup> , 4 PD
ZR-CHOP	3 (20.0%)	3 CR
R + High-Dose MTX	1 (6.7%)	PD
R + High-Dose MTX+Bendamustine	1 (6.7%)	CR
R-GOD	1 (6.7%)	PD
ZR2	1 (6.7%)	PR
R2	1 (6.7%)	PD

CR, complete remission; PR, partial remission; PD, progressive disease; MTX, methotrexate; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; ZR-CHOP, zanubrutinib + R-CHOP; ZR2, zanubrutinib + rituximab + lenalidomide; R2, rituximab + lenalidomide; R-GOD, rituximab + gemcitabine + oxaliplatin + dexamethasone; R, rituximab; Z, zanubrutinib.

<sup>a</sup>The two patients who achieved PR were evaluated only by contrast-enhanced CT at the end of treatment (one due to COVID-19-related local assessment, the other due to refusal of PET-CT for financial reasons). Since both patients subsequently maintained PFS longer than 2 years, it is possible that they eventually achieved an unconfirmed CR or CMR.



**Figure 1.** Survival analysis of patients with tWM. (A) Overall survival (OS) from the time of histologic transformation for all patients. (B) OS from the time of initial WM diagnosis for all patients. (C) OS from histologic transformation stratified by treatment regimens containing or not containing BTKi. (D) OS from initial WM diagnosis stratified by treatment regimens containing or not containing BTKi. BTKi, Bruton's tyrosine kinase inhibitor; OS, overall survival; tWM, transformed Waldenström macroglobulinemia.

First-line treatments after histologic transformation are detailed in Table 3. Among three patients with CNS involvement, two received high-dose methotrexate (MTX)-containing regimens. The third patient, who had poor performance status and concurrent severe infection, was treated with a rituximab plus lenalidomide regimen. Only one of these three patients achieved complete remission (CR).

The overall response rate to first-line therapy after transformation was 53.3% (8/15), with 33.3% (5/15) achieving CR. Among the seven patients treated with R-CHOP, the CR rate was 14.3% (1/7). Notably, two of these patients who attained partial response (PR)—with PFS of 26 and 53 months, respectively—underwent only contrast-enhanced CT for end-of-treatment assessment. It is therefore plausible that they may have eventually reached an unconfirmed CR or complete metabolic response (CMR). In contrast, all three patients treated with zanubrutinib plus R-CHOP (ZR-CHOP) achieved CR, resulting in a 100% CR rate in this subgroup.

Median follow-up time was 19 months from transformation and 45 months from initial WM diagnosis. During follow-up, 9 patients (60%) died of disease progression. Survival analysis showed a median OS of 26.0 months (95% CI: 7.3–44.7) after transformation (Figure 1A), and a median OS of 64.0 months (95% CI: 37.4–90.6) from initial WM diagnosis (Figure 1B).

No survival benefit was observed in patients without prior WM therapy ( $\chi^2 = 0.02$ ,  $p=0.88$ ). In contrast, patients who received BTKi-based regimens after transformation demonstrated significantly improved overall survival ( $\chi^2 = 7.26$ ,  $p=0.007$ ; Figure 1C). It should be noted that this group presented with more favorable baseline prognostic characteristics, including better performance status (median ECOG-PS: 1 vs. 3) and a lower proportion of high-risk IPI scores (majority high-intermediate risk vs. majority high risk in the non-BTKi group), which may have partly contributed to the observed survival advantage (Supplemental Table 1). Importantly, however, when evaluating all patients exposed to BTKi at any time point, a consistent trend toward improved OS was still observed ( $\chi^2 = 2.85$ ,  $p=0.092$ ; Figure 1D). This finding further supports a potential clinical benefit associated with BTKi-based therapy.

The addition of zanubrutinib to R-CHOP (ZR-CHOP) did not appear to introduce substantial additional toxicity beyond that expected with R-CHOP alone. In our retrospective safety analysis of the three patients receiving this regimen, adverse events were primarily hematological, consistent with the known toxicity profile of immunochemotherapy. Only one patient experienced Grade 3–4 events (neutropenia and thrombocytopenia). Common Grade 1–2 events included cytopenias and infections. One patient had a Grade 1 elevation in alanine aminotransferase. No unexpected toxicities or treatment-related deaths occurred.

## Discussion

This retrospective, single-center study analyzed 15 cases of histologic transformation from WM to DLBCL. The timing of transformation varied considerably, ranging from initial WM diagnosis to 15 years post-diagnosis. Notably, 40% of patients received no systemic therapy for WM before transformation. Transformed cases typically exhibited aggressive clinical features, with 33.3% involving immune-privileged sites including the CNS and testes. The overall prognosis was poor, with a median OS of 26 months post-transformation. However, BTKi-based immunochemotherapy regimens were associated with improved survival outcomes.

Histologic transformation in WM is uncommon. A population-based study using the SEER-17 database of 19,921 patients with indolent non-Hodgkin lymphoma (NHL), reported a cumulative transformation rate of 2.22% (36/1622) for lymphoplasmacytic lymphoma (LPL)/WM. This rate was significantly lower than those observed in splenic marginal zone lymphoma (SMZL; 6.78%, 35/516) and follicular lymphoma (FL; 5.55%, 662/11,934). Among all indolent NHL subtypes, however, transformed LPL/WM demonstrated the worst prognosis, with a 5-year OS rate of 33%. Although 42% of LPL/WM patients underwent transformation within two years of diagnosis, early transformation was not significantly associated with inferior outcomes. Consistent with our findings, this study also demonstrated that prior therapy did not significantly affect survival after transformation [10].

Approximately 75% of DLBCL cases arising from WM retain the same immunoglobulin heavy chain variable region (IGHV) rearrangement as the original WM clone, whereas the remaining 25% represent clonally unrelated events. Berendsen et al. reported a case wherein the transforming DLBCL clone was initially a minor subclone in the bone marrow at WM diagnosis but subsequently evolved into the dominant malignant population. Unlike Richter transformation (RT) in chronic lymphocytic leukemia (CLL), no consistent IGHV gene usage pattern associated with transformation in WM [5,6,11].

The hallmark genetic alterations in WM include *MYD88*<sup>L265P</sup> and *CXCR4* mutations. While *MYD88*<sup>L265P</sup> is present in over 90% of WM cases, its prevalence decreases to approximately 73% among patients who undergo histologic transformation, suggesting clonal evolution [6]. *MYD88* wild-type WM is characterized by distinct molecular features, including alterations in genes involved in NF- $\kappa$ B signaling (*TBL1XR1*, *MALT1*, *BCL10*, *NFKB2*), epigenetic regulation (e.g. *KMT2D*, *KMT2C*, *KDM6A*), and DNA damage repair (e.g. *TP53*, *ATM*) [12]. Clinically, *MYD88* wild-type status confers a five-fold increased risk of histologic transformation

compared with mutated cases [4]. *CXCR4* mutations appear to be more frequent in the transformed WM group (55%) than in non-transformed cases (30%) [6,11,13], suggesting a possible role in disease progression. During transformation of WM to DLBCL, frequent mutations are acquired in genes such as *BTG1*, *BTG2*, *CARD11*, *CD79B*, *PIM1*, and *TP53*. These mutations, which affect pathways including NF- $\kappa$ B, BCR signaling, and apoptosis, may drive the transformation process and offer potential targets for precision medicine [6,11,14]. In current study, the mutation rates of *MYD88*<sup>L265P</sup>, *CXCR4*, and *TP53* were 90%, 30%, and 40%, respectively, without clear evidence of the previously reported trend toward decreased *MYD88* and increased *CXCR4* mutation frequencies.

Both our findings and previous literature highlight a pronounced tendency for extranodal and immune-privileged site involvement in tWM [3,7,12,14,15]. A multicenter study by Durot et al. Of 235 cases of transformed WM reported CNS involvement at diagnosis in 11% of patients, with cumulative CNS relapse rates of 9.3%, 10.6%, and 12.6% at 2, 3, and 5 years, respectively. The median time to CNS relapse was 11 months, with 70% representing isolated relapses [7]. CNS involvement is characteristic of both MCD-type DLBCLs harboring *MYD88*<sup>L265P</sup> mutations and rare IgM-secreting DLBCLs [16,17]. Using droplet digital PCR, Keiichiro H. and colleagues demonstrated that *MYD88*<sup>L265P</sup> mutations could be detected in 39.1% (9/23) of bone marrow mononuclear cells from primary CNS-DLBCL patients, even without tumor infiltration [18], supporting the existence of common precursor cells (CPCs) bearing *MYD88*<sup>L265P</sup> mutation during early B-cell differentiation. Thus, regardless of clonal relatedness, *MYD88*<sup>L265P</sup> mutation may serve as a shared molecular foundation. Additional genetic alterations in *BTG1*, *BTG2*, *CD79B*, *CARD11*, *TP53*, and *PIM1* may drive further evolution and promote invasion of extranodal and immune-privileged sites [6,14,19].

Clonal evolution from WM to DLBCL may follow linear or branched trajectories. In a case reported by Berendsen et al. DLBCL lesions from testis and skin displayed distinct mutational profiles despite clonal relatedness, underscoring the spatial heterogeneity of transformed WM [6]. In such cases, circulating tumor DNA (ctDNA) analysis may provide a more comprehensive and sensitive approach for molecular disease monitoring.

BTKi has become a cornerstone of WM treatment; however, their impact on transformation risk remains unclear. In the ASPEN trial (median follow-up, 44.4 months), histologic transformation was observed in only one patient (*MYD88* wild-type) of 229 enrolled, suggesting that transformation rates may be lower in the BTKi era [20]. Moreover, BTKis exhibit multiple anti-lymphoma mechanisms in both WM and DLBCL. Mechanistically, BTKis promote autophagic degradation of ubiquitinated *MYD88*<sup>L265P</sup>, improving outcomes in MCD-type DLBCL [21]. Clinically, BTKis have demonstrated efficacy in double-expressor and extranodal DLBCL subtypes [22,23]. In our study, patients with tWM frequently exhibited extranodal involvement, double-expressor status, and non-GCB subtype—all factors associated with poor prognosis. Notably, all six patients who received BTKi-containing regimens following transformation achieved survival benefit, supporting the rationale for incorporating BTKis in tWM management. Additionally, several case reports have suggested that BTKi-based therapies may be effective in treating tWM [24,25].

Several limitations of this study should be acknowledged. First, the sample size was small, and due to the relatively recent approval of BTK inhibitors in China, many patients did not receive BTKi treatment prior to transformation, limiting generalizability. Second, while BTKi-based regimens after transformation offer the potential to target both WM and transformed clones, there is currently no standard treatment for BTKi-refractory transformed WM, highlighting an area for future research. Finally, direct comparison of outcomes between the BTKi and non-BTKi groups is constrained not only by the limited cohort size but also by imbalances in baseline prognostic factors (e.g. IPI, ECOG-PS). These differences may have influenced the observed survival outcomes and should be considered when interpreting the results.

## Conclusions

This study provides comprehensive clinical and prognostic characterization of transformed WM in a Chinese cohort. Our findings suggest that WM patients with B symptoms, elevated LDH, extensive nodal disease, or extranodal involvement—particularly of immune-privileged sites—should be carefully evaluated for histologic transformation. BTKi-based immunochemotherapy may provide significant clinical benefit in this population. However, in the era of widespread BTKi use, the true incidence of histologic

transformation, the clonal relationships between WM and DLBCL, and the mechanisms of clonal evolution remain critical areas for future prospective, multicenter investigations.

### Authors contributions

CRedit: **Yi Xia**: Data curation, Formal analysis, Funding acquisition, Resources, Writing – original draft; **Haorui Shen**: Data curation, Resources; **Yi Miao**: Data curation, Resources; **Yuxiao Zhao**: Data curation, Resources; **Hailing Liu**: Data curation, Resources; **Sanmei Wang**: Data curation, Resources; **Tian Tian**: Data curation, Resources; **Ji Xu**: Data curation, Resources; **Jianyong Li**: Conceptualization, Writing – review & editing; **Lei Fan**: Conceptualization, Supervision, Writing – review & editing.

### Disclosure statement

The authors declare no conflict of interest.

### Funding

This work was supported by the National Natural Science Foundation of China (Grant numbers 82470186 and 82170186), the Natural Science Foundation of Jiangsu Province (BK20232039), the ‘Champion Program’ of Jiangsu Province Hospital (JBG202404), the China Postdoctoral Science Foundation (2021M691336), and the Jiangsu Postdoctoral Science Foundation (2021K083A).

### ORCID

Yi Xia  <http://orcid.org/0000-0002-2197-5865>  
 Yi Miao  <http://orcid.org/0000-0003-1799-1448>  
 Hailing Liu  <http://orcid.org/0000-0002-8712-2152>  
 Jianyong Li  <http://orcid.org/0000-0002-9931-4055>  
 Lei Fan  <http://orcid.org/0000-0002-9368-4987>

### Data availability statement

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

### References

- [1] Gertz MA. Waldenstrom macroglobulinemia: 2025 update on diagnosis, risk stratification, and management. *Am J Hematol.* 2025;100(6):1061–1073. doi: [10.1002/ajh.27666](https://doi.org/10.1002/ajh.27666).
- [2] Hematology Oncology Committee of China Anti-Cancer A, Chinese Society of Hematology CMA, Chinese Working Group of Walderstrom M. [Chinese guideline for diagnosis and treatment of lymphoplasmacytic lymphoma/Walderstrom macroglobulinemia (2022)]. *Zhonghua Xue Ye Xue Za Zhi.* 2022;43(8):624–630.
- [3] Castillo JJ, Gustine J, Meid K, et al. Histological transformation to diffuse large B-cell lymphoma in patients with Waldenstrom macroglobulinemia. *Am J Hematol.* 2016;91(10):1032–1035. doi: [10.1002/ajh.24477](https://doi.org/10.1002/ajh.24477).
- [4] Zanwar S, Abeykoon JP, Durot E, et al. Impact of MYD88(L265P) mutation status on histological transformation of Waldenstrom macroglobulinemia. *Am J Hematol.* 2020;95(3):274–281. doi: [10.1002/ajh.25697](https://doi.org/10.1002/ajh.25697).
- [5] Parry EM, Roulland S, Okosun J. DLBCL arising from indolent lymphomas: how are they different? *Semin Hematol.* 2023;60(5):277–284. doi: [10.1053/j.seminhematol.2023.11.002](https://doi.org/10.1053/j.seminhematol.2023.11.002).
- [6] Berendsen MR, van Bladel DAG, Hesius E, et al. Clonal relationship and mutation analysis in lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia associated with diffuse large B-cell lymphoma. *Hemasphere.* 2023;7(11):e976. doi: [10.1097/HS9.0000000000000976](https://doi.org/10.1097/HS9.0000000000000976).
- [7] Durot E, Kanagaratnam L, Zanwar S, et al. High frequency of central nervous system involvement in transformed Waldenstrom macroglobulinemia. *Blood Adv.* 2022;6(12):3655–3658. doi: [10.1182/bloodadvances.2022007331](https://doi.org/10.1182/bloodadvances.2022007331).
- [8] 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. doi: [10.1053/j.seminhematol.2023.03.009](https://doi.org/10.1053/j.seminhematol.2023.03.009).
- [9] Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol.* 2014;32(27):3059–3068. doi: [10.1200/JCO.2013.54.8800](https://doi.org/10.1200/JCO.2013.54.8800).

- [10] Vaughn JL, Ramdhanny A, Munir M, et al. A comparative analysis of transformed indolent lymphomas and de novo diffuse large B-cell lymphoma: a population-based cohort study. *Blood Cancer J.* 2024;14(1):212. doi: [10.1038/s41408-024-01194-5](https://doi.org/10.1038/s41408-024-01194-5).
- [11] Maher N, Mouhssine S, Matti BF, et al. Molecular mechanisms in the transformation from indolent to aggressive B cell malignancies. *Cancers (Basel).* 2025;17(5):907. doi: [10.3390/cancers17050907](https://doi.org/10.3390/cancers17050907).
- [12] Hunter ZR, Xu L, Tsakmaklis N, et al. Insights into the genomic landscape of MYD88 wild-type Waldenström macroglobulinemia. *Blood Adv.* 2018;2(21):2937–2946. doi: [10.1182/bloodadvances.2018022962](https://doi.org/10.1182/bloodadvances.2018022962).
- [13] Hunter ZR, Xu L, Yang G, et al. The genomic landscape of Waldenström macroglobulinemia is characterized by highly recurring MYD88 and WHIM-like CXCR4 mutations, and small somatic deletions associated with B-cell lymphomagenesis. *Blood.* 2014;123(11):1637–1646. doi: [10.1182/blood-2013-09-525808](https://doi.org/10.1182/blood-2013-09-525808).
- [14] Boiza-Sánchez M, Manso R, Balagué O, et al. Lymphoplasmacytic lymphoma associated with diffuse large B-cell lymphoma: progression or divergent evolution? *PLoS ONE.* 2020;15(11):e0241634. doi: [10.1371/journal.pone.0241634](https://doi.org/10.1371/journal.pone.0241634).
- [15] Durot E, Tomowiak C, Michallet A-S, et al. Transformed Waldenström macroglobulinaemia: clinical presentation and outcome: a multi-institutional retrospective study of 77 cases from the French Innovative Leukemia Organization (FILO). *Br J Haematol.* 2017;179(3):439–448. doi: [10.1111/bjh.14881](https://doi.org/10.1111/bjh.14881).
- [16] Roschewski M, Phelan JD, Jaffe ES. Primary large B-cell lymphomas of immune-privileged sites. *Blood.* 2024;144(25):2593–2603. doi: [10.1182/blood.2023020911](https://doi.org/10.1182/blood.2023020911).
- [17] Cox MC, Marcheselli L, Scafetta G, et al. IgM-secreting diffuse large B-cell lymphoma: results of a multicentre clinicopathological and molecular study. *Leukemia.* 2022;36(11):2719–2723. doi: [10.1038/s41375-022-01706-x](https://doi.org/10.1038/s41375-022-01706-x).
- [18] Hattori K, Sakata-Yanagimoto M, Kusakabe M, et al. Genetic evidence implies that primary and relapsed tumors arise from common precursor cells in primary central nervous system lymphoma. *Cancer Sci.* 2019;110(1):401–407. doi: [10.1111/cas.13848](https://doi.org/10.1111/cas.13848).
- [19] Jiménez C, Alonso-Álvarez S, Alcoceba M, et al. From Waldenström's macroglobulinemia to aggressive diffuse large B-cell lymphoma: a whole-exome analysis of abnormalities leading to transformation. *Blood Cancer J.* 2017;7(8):e591–e591. doi: [10.1038/bcj.2017.72](https://doi.org/10.1038/bcj.2017.72).
- [20] 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. doi: [10.1200/JCO.22.02830](https://doi.org/10.1200/JCO.22.02830).
- [21] Phelan JD, Scheich S, Choi J, et al. Response to Bruton's tyrosine kinase inhibitors in aggressive lymphomas linked to chronic selective autophagy. *Cancer Cell.* 2024;42(2):238–252 e9. doi: [10.1016/j.ccell.2023.12.019](https://doi.org/10.1016/j.ccell.2023.12.019).
- [22] Johnson PWM, Balasubramanian S, Hodgkinson B, et al. Clinical impact of ibrutinib plus R-CHOP in untreated DLBCL coexpressing BCL2 and MYC in the phase 3 PHOENIX trial. *Blood Adv.* 2023;7(10):2008–2017. doi: [10.1182/bloodadvances.2022009389](https://doi.org/10.1182/bloodadvances.2022009389).
- [23] Geng H, Jia S, Zhang Y, et al. Efficacy and safety of zanubrutinib plus R-CHOP in treatment of non-GCB DLBCL with extranodal involvement. *Front Immunol.* 2023;14:1219167. doi: [10.3389/fimmu.2023.1219167](https://doi.org/10.3389/fimmu.2023.1219167).
- [24] Chen H, Zhao D, Wang Z, et al. Clonally related transformation from Waldenström macroglobulinemia to diffuse large B-cell lymphoma with central nervous system involvement at diagnosis: a case report and literature review. *Clin Exp Med.* 2023;23(8):5473–5476. doi: [10.1007/s10238-023-01245-4](https://doi.org/10.1007/s10238-023-01245-4).
- [25] Lindholm KE, Forsberg PA, Ewalt MD. Ibrutinib response in cutaneous transformed lymphoplasmacytic lymphoma. *EJHaem.* 2021;2(3):565–568. doi: [10.1002/jha2.253](https://doi.org/10.1002/jha2.253).