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Report of Consensus Panel 5 from the 12th International Workshop on Waldenstrom's Macroglobulinemia on the management of patients with intolerance or resistance to covalent BTK inhibitors

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ABSTRACT

Over the last decade, covalent Bruton tyrosine kinase (BTK) inhibitors have become a standard option for treating patients with symptomatic Waldenström Macroglobulinemia (WM) in the frontline or relapsed settings. However, the definition of intolerance and resistance to covalent BTK inhibitors has not been established. Understanding the best approaches to managing such patients is crucial to avoiding premature abandonment of effective therapy or pursuing futile therapies unlikely to be effective in controlling symptomatic disease progression. With the advent of noncovalent BTK inhibitors and BCL2 antagonists, in addition to clinical trials evaluating phospholipid-drug conjugates, antibody-drug conjugates, and bispecific antibodies, the present Consensus Panel 5 aims to establish working definitions for intolerance and resistance to covalent BTK inhibitors, as well as provide strategies to identify and manage these issues not infrequently encountered in clinical practice.

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Introduction

Covalent Bruton tyrosine kinase (BTK) inhibitors are standard therapies for patients with symptomatic Waldenström macroglobulinemia (WM) worldwide [1–13]. The United States Food & Drug Administration and the European Medicines Agency approved

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Table 1
Efficacy data from prospective clinical trials evaluating covalent BTK inhibitors in WM patients.

Agent	N	Setting	ORR	≥PR rate	≥VGPR rate	PFS
Ibrutinib [1,7]	63	RR	91%	79%	30%	5-year: 54%
Ibrutinib [3,9]	30	TN	100%	83%	30%	4-year: 73%
Ibrutinib plus rituximab [2,8]	75	TN/RR	92%	76%	29%	54-month: 68%
Ibrutinib plus venetoclax [35]	45	TN	100%	96%	42%	24-month: 76%
Acalabrutinib [4,12]	106	TN/RR	93%	78%	30%	66-month: 52%
Zanubrutinib [5,13]	101	TN/RR	98%	81%	36%	42-month: 78%
Tirabrutinib [6,11]	27	TN/RR	96%	93%	30%	2-year: 93%
Orelabrutinib [10]	66	RR	89%	81%	21%	1-year: 89%

ORR = overall response rate; PFS = progression-free survival; PR = partial response; RR = relapsed or refractory; TN = treatment naïve; VGPR = very good partial response.

ibrutinib monotherapy, ibrutinib in combination with rituximab, and zanubrutinib monotherapy for treating patients with WM. Tirabrutinib and orelabrutinib were approved in Japan and China, respectively, in 2020.

Table 1 summarizes the efficacy data of prospective clinical trials of covalent BTK inhibitors in patient with WM. Along with chemoimmunotherapy, covalent BTK inhibitors are among the most used agents to treat WM [14]. However, despite the deep and durable responses frequently observed with covalent BTK inhibitor therapy, patients with WM can develop intolerance, or their disease can acquire resistance to these agents. Therefore, the approach and management of these patients represent a current unmet need.

During the 12th International Workshop for WM (IWWM-12), Consensus Panel 5 was formed to establish definitions for patients with WM who become intolerant or whose disease develops resistance to covalent BTK inhibitors and provide strategies for management.

Methodology

The Chairs (JJC and MLP) drafted a series of critical 1uestions before the initial in-person meeting and discussion. The members of the Consensus Panel were chosen based on their expertise and/or interest in the topic. The Critical Questions were presented at the initial in-person meeting on October 19, 2024, at IWWM-12 in Prague, Czechia. The Consensus Panel approved the Critical Questions before the discussion. All the members of the Consensus Panel participated actively in the debate. An initial draft document summarizing the outcomes of the initial discussion was generated and distributed to the members of the Consensus Panel for review on December 31, 2024. A virtual meeting took place on January 15, 2025, to address the members' comments and further discuss the contents of this Report. The final report was sent to the members of the Consensus Panel on January 31, 2025, for their final review. All the members reviewed and approved the final Report. No external or financial support was received for the creation of this Report.

Critical questions

1. How do we define covalent BTK inhibitor intolerance?

Covalent BTK inhibitor therapy can be associated with unique on-therapy adverse events that include increased risk of spontaneous bruising or bleeding following surgery or trauma, atrial fibrillation, hypertension, gastrointestinal symptoms (e.g., diarrhea) or other gastrointestinal symptoms, cytopenias, arthralgia or myalgia, and skin eruptions, among others. Table 2 presents notable grade ≥3 adverse events reported in clinical trials evaluating covalent BTK inhibitors in patients with WM.

The Consensus Panel agreed that intolerance to a covalent BTK inhibitor has not been formally defined. The Panel defined BTK inhibitor intolerance as the inability to continue administering the BTK inhibitor at therapeutic doses (that effectively control the WM) due to persistent adverse events despite appropriate mitigation strategies, including appropriate supportive care measures and dose reduction. Such events must be deemed related to the agent and not attributable to, or exacerbated by, concurrent medication or medical condition and significantly impact the patient's activities of daily living, quality of life, or lifestyle. Upon further deliberation, the panel members agreed on absolute contraindications to continuing the use of a covalent BTK inhibitor, namely the occurrence of life-threatening events such as an anaphylactic reaction to the inhibitor, intracranial (or other life-threatening) hemorrhage, or ventricular arrhythmia while using the agent. In these patients, mere dose reduction is not a sufficient mitigating measure.

The Consensus Panel is aware that deeming a patient intolerant relies on clinical judgment in the absence of the above absolute contraindications to covalent BTK inhibitors. We encourage a

Table 2
Selected grade ≥3 adverse events reported in prospective clinical trials evaluating covalent BTK inhibitors in WM patients.

Adverse event	Ibrutinib RR	Ibrutinib TN	Ibrutinib plus rituximab	Ibrutinib plus venetoclax	Acalabrutinib	Zanubrutinib	Tirabrutinib	Orelabrutinib
Anemia		7%	12%	2%		12%		
Neutropenia	16%	10%	13%	29%		24%	22%	11%
Thrombocytopenia	11%	7%	1%	2%		11%		6%
Infections	6%	10%	29%	2%		22%		4%
Atrial fibrillation*	10%	20%	16%	6%	13%	8%	7%	
Hypertension		10%	15%	2%	4%	10%		
Cardiac arrest/ventricular arrhythmia*		3%		9%		1%		
LFT elevation		10%		2%				
Rash		7%					8%	
MSK symptoms		3%	4%	4%	1%			
Bleeding		3%		2%	6%	9%	8%	
GI symptoms				6%	4%	3%		

* Any grade.
RR = relapsed or refractory; GI = gastrointestinal; LFT = liver function test; MSK = musculoskeletal; TN = treatment naïve.

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direct and frank discussion between the patient and the treating clinician on the cause of the adverse event(s), the probability that the adverse event is related to the agent, the likelihood that the event will improve or resolve after stopping therapy, and the impact of the event on the patients' quality of life. In addition, the risk of sub-optimal disease control or the emergence of adverse events with a different BTK inhibitor must be considered before substituting with a next-generation BTK inhibitor or abandoning covalent BTK inhibitor therapy.

2. What are the best options for covalent BTK inhibitor-intolerant patients?

The Panel recommends against switching between covalent BTK inhibitors in patients whose disease is responding, in the absence of intolerance as defined above.

Once an adverse event is deemed related to the covalent BTK inhibitor and its impact on the patient's quality of life has been established, it can be addressed with symptom management, appropriate supportive care measures, dose reductions, temporary holds, or permanent discontinuation of therapy.

The Consensus Panel encourages clinicians to use symptomatic management as an initial step in caring for patients with WM experiencing an adverse event to the covalent BTK inhibitor. Examples of symptomatic management include using medications to ease the impact of the adverse event, like acetaminophen for headaches, loperamide for diarrhea, physical therapy for arthralgia or back pain, topical steroids for skin rash, and granulocyte colony-stimulating factor for neutropenia. If the adverse event is not manageable, timely referral to the appropriate specialist based on the patient's symptomatology is a reasonable next step (e.g., dermatologist for rash).

Temporarily holding therapy may be helpful when the relationship between the event and the agent is unclear or doubtful. As most covalent BTK inhibitors have a median half-life of 4-6 hours, events associated with BTK inhibitor therapy could improve or resolve within 3-7 days of stopping treatment. Temporary cessation is universally recommended before and after endoscopic or surgical procedures or post-trauma to minimize the risk of bleeding.

Dose reductions should be the initial standard approach to managing adverse events associated with covalent BTK inhibitors. In a retrospective study of 353 patients with WM taking ibrutinib 420 mg orally once daily, 96 (27%) required dose reductions to manage adverse events [15]. Dose reductions were more common in patients aged ≥65 years and women. After the dose reduction, two-thirds of the patients experienced improvement or resolution of the adverse event, while the prereduction response was sustained or even deepened in 80%. More than half of the patients with musculoskeletal and gastrointestinal symptoms, hypertension, skin/hair/nail/mucosal changes, and liver function test abnormalities experienced improvement or resolution, compared with a minority of patients who experienced BTK inhibitor-related bleeding, atrial fibrillation, neurological symptoms, or edema. Furthermore, dose reductions did not negatively impact patients' outcomes, though longer follow-up is needed.

Switching therapy to another covalent BTK inhibitor, if available, is a reasonable next step if symptomatic management and dose reductions are ineffective in controlling adverse events. A phase II study evaluated switching therapy from ibrutinib or acalabrutinib to zanubrutinib in 67 intolerant patients with hematologic malignancies, including WM [16]. Most intolerance events (70% for ibrutinib and 80% for acalabrutinib) did not recur after switching to zanubrutinib. Of the recurring events, 79% for ibrutinib and 33% for acalabrutinib recurred at a lower intensity on zanubrutinib. No events recurred at a higher severity on zanubrutinib.

Another phase II study evaluated acalabrutinib in 60 patients with chronic lymphocytic leukemia (CLL) intolerant to ibrutinib [17]. Intolerance was defined as the persistence of grade 3 or 4 adverse events or the persistence or recurrence of grade 2 adverse events despite dose modification or interruption. Adverse events were graded based on the Common Terminology Criteria for Adverse Events version 4.03 (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm). Forty percent of the patients experienced similar events on acalabrutinib as on ibrutinib. Of these, 67% occurred at a lower grade, 30% at the same grade, and 3% at a higher grade on acalabrutinib than on ibrutinib.

Switching from second-generation covalent BTK inhibitors to ibrutinib because of intolerance could be considered based on the unpublished collective experience of members of the Panel.

When switching from a dose-reduced to another covalent BTK inhibitor, the Consensus Panel recommends starting the new agent at the standard dose and considering dose reduction if adverse events develop again.

In situations, where switching to another covalent BTK inhibitor is unreasonable or inappropriate, discontinuing covalent BTK inhibitor therapy and considering a drug with a different mechanism of action would be indicated. The Consensus Panel recommendations regarding switching treatments from covalent BTK inhibitors are provided later in this report.

Fig. 1 shows a recommended algorithm for approaching covalent BTK inhibitor intolerance.

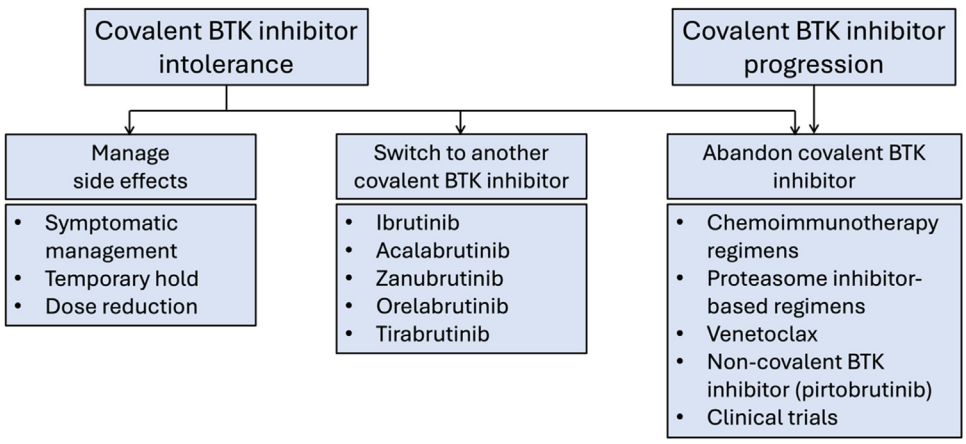

Fig. 1. Recommended algorithm for approaching intolerance or resistance to covalent BTK inhibitor therapy in WM patients. BTK = Bruton tyrosine kinase inhibitor.

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3. How do we define covalent BTK inhibitor resistance?

The Consensus Panel defined resistance as meeting the criteria for disease progression in patients who had previously achieved at least a minor response while on covalent BTK inhibitor therapy (relapsed disease) or meeting the criteria for a response no deeper than stable disease without clinical benefit after at least 6 months of covalent BTK inhibitor therapy (refractory disease). A unique scenario for relapsed disease includes the development of clinically significant cytopenia due to bone marrow infiltration without a corresponding increase in the serum IgM level and without an alternative etiology.

The criteria for disease progression established by the IWWM-11 are defined by a ≥25% increase in serum IgM levels with a minimum increase of 500 mg/dl from nadir, any new lesion >1.5 cm in any axis, or unequivocal evidence of an increase by >50% in any axis to >1.5 cm in size of previously involved extramedullary disease sites from their nadir measurements, or any new lesion consistent with transformed disease [18].

Importantly, the increase in serum IgM level because of disease progression should occur in the absence of drug holds or temporary discontinuation of therapy and should not be confused with an IgM rebound, which might be associated with withdrawal symptoms in 20% of patients temporarily holding BTK inhibitors [19]. IgM rebound and withdrawal symptoms improve upon reinitiation of the BTK inhibitor. Similarly, an IgM flare, typically seen after therapy with rituximab, should be differentiated from disease progression [20,21]. Two sequential measurements are required to confirm disease progression if serum IgM level is used. The demonstration of disease progression by imaging does not require confirmation. Patients meeting disease progression criteria can continue covalent BTK inhibitor therapy for ongoing clinical benefit (See Section 5).

4. Should *BTK* mutational testing be performed in WM patients progressing on covalent BTK inhibitors?

The acquisition of somatic mutations in *BTK* (e.g., *BTK C481S*, *L258W*) has been associated with disease resistance to covalent BTK inhibitors in patients with CLL, mantle cell lymphoma, and WM [22–24]. Several commercial panels are available to assess *BTK* mutations in patients progressing on covalent BTK inhibitors. However, the usefulness of these tests in guiding the management of these patients is not well established. The median time from therapy initiation to the acquisition of these mutations and from mutation acquisition to the development of disease resistance by hematological parameters or symptomatic disease progression in WM are unknown. Furthermore, resistance to a BTK inhibitor can develop without detectable *BTK* mutations. Deletions in 6q and 8p and recurring mutations in *PCLG2*, ubiquitin ligases, innate immune signaling, and TLR/MYD88 pathway regulators can drive resistance to BTK inhibitors [25].

The Consensus Panel agrees that testing for *BTK* mutations might not alter patient management and should not be routinely recommended in clinical practice. The acquisition of *BTK* mutations does not necessarily indicate a need for immediate therapy change in patients with disease progression who are otherwise asymptomatic with normal hematological parameters. At the same time, the absence of *BTK* mutations would not alter the decision to change therapy in patients with symptomatic disease progression.

The Consensus Panel supports ongoing research on *BTK* mutations and other resistance mechanisms to covalent BTK inhibitors, such as mutations in *CXCR4, TP53, and PLCγ2* [23,26–30]. Specifically, the members encourage the inclusion of BTK inhibitor resistance panels in clinical trials evaluating BTK inhibitors alone or in combination.

5. What are the best options for treating patients with covalent BTK inhibitor-resistant disease?

Available data suggest that many patients with WM who stop covalent BTK inhibitor therapy could experience rapid disease progression, known as IgM rebound, characterized by a rapid increase in serum IgM levels followed by symptomatic disease progression. A single-institution study showed that the rate of IgM rebound was 36% following the discontinuation of ibrutinib monotherapy [31]. Another study of WM patients with acquired disease resistance to ibrutinib monotherapy showed that 29 of 48 patients (60%) experienced an IgM rebound upon stopping therapy, with a median time to rebound of 27 days [32]. The investigators were unable to identify factors predictive of IgM rebound.

In the same study, 48 of 51 patients (94%) required salvage therapy, with a median time to salvage therapy of 18 days, and 10 of 29 patients (34%) who developed symptomatic hyperviscosity were initially managed with plasmapheresis, with a median time to symptomatic hyperviscosity of 29 days. The overall response rate to salvage therapy after ibrutinib discontinuation was 56%. Only patients with quadruple-exposed disease (rituximab, proteasome inhibitor, alkylating agent, and ibrutinib) had a lower probability of response than those who had received fewer lines of therapy (33% vs 73%; $P = .01$).

In addition to rituximab-containing regimens, BCL2 antagonists and noncovalent BTK inhibitors are potentially effective in patients with symptomatic progression on covalent BTK inhibitors.

In a prospective phase II study of 32 previously treated patients with WM, of whom 16 (50%) were previously exposed to covalent BTK inhibitor, therapy with the BCL2 antagonist venetoclax (ramped-up dose to 800 mg orally once daily for a maximum of 2 years) induced a major response rate of 81%, a VGPR rate of 19%, and a median PFS of 30 months [33]. Previous exposure to a covalent BTK inhibitor was associated with a numerically lower VGPR rate (13% vs 27%; $P = .33$) and a longer time to response (4.5 vs 1.4 months; $P < .01$) but no different PFS compared with patients not previously exposed. Common grade ≥3 adverse events included neutropenia and gastrointestinal symptoms (e.g., diarrhea, constipation, and dyspepsia). Venetoclax therapy requires monitoring for tumor lysis syndrome during the dose ramp-up.

A prospective phase II study evaluated the safety and efficacy of the noncovalent BTK inhibitor pirtobrutinib in 78 previously treated WM patients [34]. In the subset of 55 patients previously exposed to ≥1 covalent BTK inhibitor, the major response rate was 64%, the VGPR rate was 24%, and the median PFS was 20 months. The most frequent grade ≥3 adverse event was neutropenia, with low rates of grade ≥3 hypertension, hemorrhage, and atrial fibrillation.

Based on the above, the Consensus Panel recommends that patients with covalent BTK inhibitor-resistant disease who meet the treatment criteria receive standard therapies to which they had not previously been exposed, such as chemoimmunotherapy, proteasome inhibitor-based therapies, BCL2 antagonists, or noncovalent BTK inhibitors, if available. Ideally, there should not be significant delays in initiating a new treatment regimen in patients with disease progressing on a BTK inhibitor. In cases of intolerance, patients must be monitored frequently when the BTK inhibitor is stopped, and a new treatment regimen should be initiated immediately or promptly. High-dose chemotherapy followed by autologous stem cell transplant could be considered in the appropriate setting. Switching to another covalent BTK inhibitor is not recommended under these circumstances, as the development of resistance to one covalent BTK inhibitor (e.g., *BTK C481S*) will render other covalent BTK inhibitors ineffective.

WM patients with disease progression on BTK inhibitors who meet the criteria to initiate the next line of therapy should be

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Table 3
Selected clinical trials evaluating novel agents or combinations in patients with WM previously exposed to covalent BTK inhibitors.

ID	Agent(s)	Mechanism of action
NCT02952508	Iopofosine I-131	Radioconjugate
NCT04728893	Nemtabrutinib	Noncovalent BTK inhibitor
NCT04830137	NX-2127	BTK/IKZ-F1 degrader
NCT05006716	BGB-16673	BTK degrader
NCT05131022	NX-5948	BTK degrader
NCT05190705	Loncastuximab tesirine	Antibody-drug conjugate
NCT05734495	Pirtobrutinib + venetoclax	Noncovalent BTK inhibitor + BCL2 antagonist
NCT05952037	Sonrotoclax	Second generation BCL2 antagonist
NCT06510491	Epcoritamab	Bispecific antibody

BTK = Bruton tyrosine kinase; IKZ-F1 = Ikaros; BCL2: B-cell lymphoma 2.

considered for clinical trials if available. Ongoing clinical trials evaluate noncovalent BTK inhibitors alone or in combination with other agents, second-generation BCL2 antagonists, BTK degraders, antibody-drug conjugates, bispecific antibodies, and chimeric antigen receptor T-cells. A list of selected clinical trials in WM patients previously exposed to covalent BTK inhibitors active as of February 2025 is shown in Table 3.

The Consensus Panel does not recommend moving to the next line therapy in otherwise asymptomatic patients meeting disease progression criteria on covalent BTK inhibitor therapy. Therefore, covalent BTK inhibitor therapy can continue beyond progression if the patients do not meet the requirements for symptomatic disease (e.g., progressive cytopenia, symptomatic extramedullary disease, or serum IgM levels worrisome for impending hyperviscosity), but the plan for the subsequent line of treatment should be in place.

6. Should we overlap therapies when switching from covalent BTK inhibitors to another therapy to avoid withdrawal symptoms or disease rebound?

In a retrospective study of patients who discontinued ibrutinib therapy because of symptomatic progression, patients who received salvage therapy within 1 week of discontinuation of ibrutinib had significantly lower probability of IgM rebound (29% vs 76%; $P = .005$) and higher probability of their disease responding to the subsequent therapy than patients who received salvage therapy >1 week later (75% vs 45%; $P = .03$) [32]. Continuing ibrutinib concurrently with salvage therapy was associated with a lower likelihood of IgM rebound (17% vs 69%; $P = .03$) and a higher overall response rate than without treatment overlap (100% vs 49%; $P = .01$).

The Panel agreed that overlapping covalent BTK inhibitor therapy and subsequent salvage therapy is reasonable and can be used per individual practice.

When switching to a rituximab-containing regimen, the covalent BTK inhibitor may be continued for 1 to 2 cycles before discontinuation to allow the subsequent therapy to take effect, as an IgM rebound is still possible during that period. Symptomatic hyperviscosity due to an IgM rebound should be managed promptly with plasmapheresis. When transitioning to a noncovalent BTK inhibitor like pirtobrutinib, the final dose of the covalent BTK inhibitor may be administered the day before initiating pirtobrutinib, and overlapping is not required.

When switching from ibrutinib to venetoclax, the last dose of ibrutinib can be taken the day before commencing venetoclax, as concurrent use of ibrutinib and venetoclax was associated with a higher-than-expected rate of life-threatening ventricular arrhythmia in a prospective study involving previously untreated patients with WM [35]. Clinical trials combining next-generation covalent and noncovalent BTK inhibitors with BCL2 antagonists are ongoing.

Conclusion

With the increasing use of covalent BTK inhibitors to treat patients with WM, managing intolerance and resistance to these agents is essential.

Based on the current knowledge, the Consensus Panel provides the following summary of recommendations:

1. Covalent BTK inhibitor intolerance is the inability to continue administering the agent at therapeutic doses due to unmanageable adverse events despite using appropriate mitigation strategies, including dose reduction.
2. Symptom management, temporary holds, dose reductions, switching to another covalent BTK inhibitor, or abandoning covalent BTK inhibitor therapy are reasonable approaches to managing intolerance.
3. Covalent BTK inhibitor resistance is defined as meeting the IWWM-11 criteria for disease progression while on therapy after an initial response (relapsed disease) or stable disease without clinical benefit after 6 months of treatment (refractory disease).
4. The information gathered from assessing *BTK* and other resistance-associated mutations might not alter the clinical management of intolerant or resistant patients, and testing is not routinely recommended outside of clinical trials.
5. Patients experiencing symptomatic disease progression while on a covalent BTK inhibitor should receive other available therapies to which they have not previously been exposed, such as chemoimmunotherapy, proteasome inhibitor-based therapies, BCL2 antagonists, noncovalent BTK inhibitors, or enrollment in clinical trials when available. Switching to another covalent BTK inhibitor is not appropriate in this setting.
6. Overlapping covalent BTK inhibitor therapy and subsequent salvage therapy to avoid symptomatic IgM rebound is optional and depends on individual practices.

Several novel targeted agents are under clinical development in patients with WM previously exposed to covalent BTK inhibitors, including the noncovalent BTK inhibitor nemtabrutinib, the novel BCL2 antagonist sonrotoclax [36], and the BTK degraders BGB-16673 [37], NX-2127, and NX-5948. BGB-16673 has shown activity in patients with WM who have progressed on both covalent and noncovalent BTK inhibitors. The all-oral, finite-duration therapy combination of pirtobrutinib and venetoclax is also under investigation [38]. Of special interest is the introduction of immunotherapy in treating WM, including the phospholipid-drug radio-conjugate iopofosine I-131 [39], the anti-CD19 antibody-drug conjugate loncastuximab tesirine [40], the anti-CD20/CD3 bispecific antibody epcoritamab [41], and chimeric antigen receptor T-cell therapy. The positioning of these agents in the treatment algo-

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rithm of patients with WM will depend on the efficacy and safety profile of these agents.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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CRediT authorship contribution statement

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