The Management of Relapsed or Refractory Waldenström's Macroglobulinemia

Ramón García-Sanz, MD, PhD[a,b,*], Alessandra Tedeschi, MD[a,b]

KEYWORDS

- Waldenström's macroglobulinemia • Salvage therapy • Chemoimmunotherapy
- Bruton tyrosine kinase inhibitors

KEY POINTS

- In Waldenström's Macroglobulinemia, the cure is still an unmet challenge.
- Combinations with alkylating agents and/or purine analogs and monoclonal antibodies, Bruton's tyrosine kinase inhibitors, and proteasome inhibitors, are treatment possibilities for relapsed and refractory patients.
- New additional agents can be seen on the horizon as potential effective therapies, including new BTK inhibitors, BCL2 inhibitors, radioconjugated drugs, and CAR T-cells.
- The best therapy in the 2nd line and beyond in Waldenström's Macroglobulinemia patients depends on the prior therapies and their results in terms of effectiveness and toxicity.

INTRODUCTION

The current consensus in Waldenström's macroglobulinemia (WM) states that diagnosis requires the following criteria: the presence of infiltration of clonal lymphoplasmacytic cells documented by bone marrow (BM) biopsy (lymphoplasmacytic lymphoma, LPL) and presence of serum monoclonal immunoglobulin M (IgM), irrespective of M-protein size.[1,2] However, fifth WHO classification still defines IgM monoclonal gammopathy of undetermined significance (IgM-MGUS) by the presence of a serum IgM paraprotein below 30 g/L, BM lymphoplasmacytic infiltration <10%,

[a] Department of Hematology, University Hospital of Salamanca, Research Biomedical Institute of Salamanca (IBSAL), Accelerator Project, Centro de Investigación Biomédica en Red-Cáncer (CIBERONC) CB16/12/00369 and Center for Cancer Research-IBMCC (USAL-CSIC), Paseo de San Vicente, 58-182, Salamanca 37007, Spain; [b] Department of Hematology, Niguarda Cancer Center, ASST Grande Ospedale Metropolitano Niguarda, Milano, Italy
* Corresponding author. Department of Hematology, University Hospital of Salamanca, Building I-J, Floor 3, Laboratory of HLA and molecular biology, Paseo de San Vicente, 58-182, Salamanca 37007, Spain.
E-mail address: rgarcias@usal.es

Hematol Oncol Clin N Am 37 (2023) 727–749
https://doi.org/10.1016/j.hoc.2023.04.006 **hemonc.theclinics.com**

and no evidence of end-organ damage related to the underlying lymphoproliferative disorder.[3] Both classifications stress the importance of the mutational landscape in WM, especially because genomics greatly impact the response to several therapies.

WM was considered as an intermediate step between mutated chronic lymphocytic leukemia (B-CLL) and multiple myeloma (MM), but the discovery of the *MYD88*^{L265P} mutation[4] contributed to separation of these entities.[5] The estimated incidence of WM is 3.6 to 5.5 cases per million person-years at risk in Europe and the United States.[6,7] Because of the rarity of this disease, we lack extensive trials evaluating therapies for WM, current therapies were mainly derived from B-CLL and MM. Things have changed, and now we have novel trials with appreciable numbers of patients with WM.

DEFINITION RELAPSED AND REFRACTORY WALDENSTRÖM'S MACROGLOBULINEMIA

When we face a patient with suspected relapsed or refractory WM (RRWM), we have to follow progressive disease criteria that, according to the 2006 definition, is categorized by >25% increase in serum monoclonal IgM by protein electrophoresis, confirmed in a second measurement, or by the progression of clinically significant findings caused by disease (anemia, thrombocytopenia, leukopenia, or bulky adenopathy/organomegaly) or symptoms (unexplained recurrent fever >38.4°C, drenching night sweats, ≥10% weight loss, hyperviscosity, neuropathy, or symptomatic cryoglobulinemia) attributable to WM.[8]

These criteria were reviewed in 2013[9] due to the increase of complete responses (CR) and very good partial responses (VGPR) reported with the updated therapeutic combinations. As in the International Workshop of WM held in 2002 in Athens,[10] it was again stressed that progression should not necessarily be followed by treatment when this is defined solely based on increasing IgM concentrations. The reappearance of monoclonal IgM protein or recurrence of BM involvement, lymphadenopathy/splenomegaly, or symptoms attributable to active disease defined a relapse from CR. Progression from a partial response (PR) or minor response was defined by >25% increase from the lowest serum IgM level. The development of new signs and symptoms of the disease, including Bing–Neel syndrome and histological transformation, was also considered evidence of disease progression.

CURRENT TREATMENT OPTIONS FOR RELAPSED/REFRACTORY WALDENSTRÖM'S MACROGLOBULINEMIA

Therapy should be initiated in the event of a symptomatic relapse or refractory disease.[11] The treatment depends on different factors that will be reviewed at the end of this review, but no consensus on a preferred regimen exists.[12] A retrospective study with 454 European patients with WM demonstrated that the median progression-free survival (PFS) after first-line therapy was only 29 months. Still, the median OS had not been achieved and the 10-year OS was 69%.[13] This means that second-line and subsequent therapies are very effective in maintaining patients mortality free from WM. In addition, PFS was shorter in patients treated with monotherapy compared to combinations,[13] which reinforce the view that monotherapy should be restricted to a few specific patients, while most should receive combination therapy, especially in second line.[14] This view changed when Bruton tyrosine kinase inhibitors (BTKi) demonstrated high efficacy in monotherapy for patients with RRWM.[15,16]

Table 1
Anti-CD20 combinations with conventional drugs in Waldenström's macroglobulinemia

Study	N		Regimen	ORR	MRR	VGPR + CR	mR	FU	OS	Comments
	Untreated	Treated								
Souchet et al,[21] 2016	25	57	*R* 375 mg/m^2 IV D1, *F* 40 mg/m^2 po D1–3, *Cy* 250 mg/m^2 po D1–3 ≥2 courses	85%	77%	42%	8%	PFS: 67% at 4 y	90% at 3 y	Grade 3–4 neutropenia, thrombopenia, and anemia of 43%, 13%, and 9%, respectively. Four cases of infection leading to treatment discontinuation
Tedeschi et al,[22] 2012	28	15	*R* 375 mg/m^2 IV D1, *F* 25 mg/m^2 po D2–4, *Cy* 250 mg/m^2 po D2–4 4–6 courses	87%	69%	13%	5%	DR: +14 mo	+20	Neutropenia in 63% Late improvement of responses was observed
Tedeschi et al,[20] 2013	-	40	*R* 375 mg/m^2 IV D1, *F* 25 mg/m^2 po D2–4, *Cy* 250 mg/m^2 po D2–4 4–6 courses	80%	80%	33%	0%	EFS 77 mo	NR	Neutropenia ≥3 (87%), anemia and thrombopenia ≥3 (28%), infections ≥3 (15%)
Laszlo et al,[18] 2010	16	13	*R*, 375 mg/m^2 iv D1 *Cl*, 0.1 mg/kg sc, D1–5 4 courses	90%	79%	24%	10%	-	-	Grade 3–4 neutropenia, 37%; 14% of infections. hCNT1 high expression correlated with the best responses.
Abonour, Buske, Ioakimidis et al[35–37]	47	10	*R* 375 mg/m^2 IV, D0 *Cy* 750 mg/m^2 IV, D1 *Dox* 50 mg/m^2 IV, D1 *V* 1.4 mg/m^2 IV (max 2) D1 *P* 100 mg/m^2 PO D1–5 6–8 courses, every 21 D	95%	71%	14%	10%	PFS: +20 mo	+36	Neutropenia 3–4 72%. Infections 6%. Alopecia 84%, Nausea/vomiting 36%, mucositis 36%

(*continued on next page*)

Table 1
(*continued*)

Study	N		Regimen	ORR	MRR	VGPR + CR	mR	FU	OS	Comments
	Untreated	Treated								
Leblond et al,[19] 2001	-	45	*Cy* 750 mg/m^2, D1 *Dox* 25 mg/m^2, D1 *P* 40 mg/m^2/day, D1–50 ~6 courses	-	11%	-	-	3 mo	8 mo	>2 Infections (2%), 1 mucositis (4%), and 1 alopecia (5%)
Paludo et al,[25] 2017	-	50	*Dex* 20 mg/m^2 po D1, *R* 375 mg/m^2 IV D1, *Cy* 200 mg/m^2/day po, D1–5 ~6 courses	87%	68%	4%	19%	FU: 51 mo PFS 32%	74% at 4 y	Grade 3–4 neutropenia, 20%; thrombopenia 7%; infections 3%. Treatment was shortened in 11% due to toxicity.
Arulogun et al,[26] 2020	139	111	*R* 375 mg/m^2, D1 *Benda*, 70–90 mg/m^2, D1–2 ~6 courses	84%	74%	24%	10%	82% at 2 y	-	Toxicity-related treatment truncation 35%
Treon et al,[27] 2011		30	*Benda* 90 mg/m^2, D1–2 ± *R* 375 mg/m^2, D1 ± (n = 24) *O* 1000 mg, D1 (n = 6)	83%	66%	17%	17%	13 mo	-	Myelosupression (13%), infection (7%) and hypersensitivity (7%)
Tedeschi et al,[28] 2015	-	71	*R* 375 mg/m^2, D1 *Benda*, 70–90 mg/m^2, D1–2 ~6 courses	80%	75%	23%	6%	NR at 19 mo	72% at 4 y	Neutropenia (13%), infections (15%), infusion-related reactions (7%). No flare
Paludo et al,[29] 2018	16	44	*R* 375 mg/m^2, D1 *Benda*, 90 mg/m^2, D1–2 ~6 courses	95%	82%	41%	13%	PFS: 88% at 2 y	–	Neutropenia (11%), infections (5%), thrombocytopenia (2%)

Abbreviations: Benda, bendamustine; Cl, cladribine; CR, complete response; Cy, cyclophosphamide; D, day; Dox, doxorubicin; DR, duration of response; Dx, dexamethasone; F, fludarabine; FU, follow-up; HCNT1, human concentrative nucleoside transporter 1; iv, intravenous; mR, minor response; O, obinutuzumab; ORR, overall response rate; OS, overall survival; P, prednisone; po, per os; PR, partial response; R, rituximab; sc, subcutaneous; TTP, time to tumor progression; V, vincristine; VGPR, very good partial response.

COMBINATIONS WITH CONVENTIONAL CHEMOTHERAPY

Combinations with Nucleoside Analogs

Nucleoside analogs (fludarabine, cladribine) demonstrated high efficacy in treatment-naïve and RR patients,[17–20] especially when combined with cyclophosphamide and rituximab. The overall response rate (ORR), defined as CR + VGPR + PR + minor response (mR), usually exceeds 80%, including a CR rate ~20% (**Table 1**). The median time to response (TTR) is < 3 months and median PFS ≥3 years.[18,21,22]

The major disadvantages of purine analogs are the hematologic toxicity and immunosuppressive complications,[11,17,21–23] and a potential increase in Richter's transformation and secondary myelodysplasia (~10%),[23,24] which has relegated the use of these drugs in WM.

Combinations with Alkylating Agents

Alkylating agents (chlorambucil and cyclophosphamide) have been extensively used in monotherapy or combination with steroids.[17] The combination of dexamethasone, rituximab, and cyclophosphamide (DRC) is one of the most popular regimens used as first-line treatment.[13] Moreover, it is also effective in the relapsed population, where it can render an ORR of 87%, with 4% VGPR, 64% PR, and 19% mR.[25]

Bendamustine has been used in both untreated and treated patients with favorable results. The biggest series in the RRWM population included 111 patients treated with rituximab and bendamustine (R-Benda) who were retrospectively evaluated; the major response rate (MRR) and ORR were 74% and 84%, respectively, with a combined CR/VGPR rate of 24%. After a median follow-up of 37 months, only 43% of patients had progressed.[26] Other studies evaluating R-Benda have provided similar results with hematologic adverse events (AEs) as the most relevant safety concerns (see **Table 1**).[27–29] Accordingly, R-Benda is considered an effective treatment but should be used with caution in frail or elderly patients, in whom frequent hospitalizations, infections, and cardiovascular events may be a challenge.[30]

Combinations with Proteasome Inhibitors

Proteasome inhibitors (PIs) have become an important therapeutic strategy in monoclonal gammopathies. Data supporting their use have led to approval for using bortezomib, carfilzomib, and ixazomib in the United States and Europe.[31] These drugs inhibit the ubiquitin-proteasome pathway (UPP), essential for cell survival. UPP inhibition results in toxic protein accumulation for the cells, especially for those specialized in protein production, such as plasma and lymphoplasmacytic cells.

Bortezomib

As a single drug, bortezomib provides 46% to 60% major responses (MRs) in patients with RRWM[32–35] at the conventional dose of 1.3 mg/m^2 (**Table 2**). Bortezomib is generally well tolerated, with usually predictable toxicities, including thrombocytopenia, fatigue, nausea, peripheral neuropathy (PNP), myalgia, non-neutropenic infections, diarrhea, and grade 3–4 constipation in up to 20% of patients, which are manageable with dose reductions or discontinuations (~40% of patients).

Results improved by adding rituximab. A total of 37 patients with RRWM were treated with bortezomib once weekly (1.6 mg/m^2) with rituximab weekly (375 mg/m^2) during courses 1 and 4.[36] The ORR was 81%, including 2 patients (5%) who achieved CR/VGPR and 17 (46%) PR. The most frequent grade 3 toxicity was hematological but manageable, and without relevant PNP. Thanks to these results, bortezomib was successfully moved to first line of therapy.[37–39]

Table 2
Combinations with proteasome inhibitors in Waldenström's macroglobulinemia

First Author Ref	N	Therapy	Cycles	ORR	MRR	VGPR + CR	Outcome	OS	Grade ≥3 Toxicity
Dimopoulos et al,[32] 2005	10	B	4	100%	60%	10%	PFS 40% at 1 y	-	Neutropenia (10%), thrombocytopenia (20%), PNP (20%), fatigue (20%), Ileus (30%)
Chen et al,[104] 2007	27	B	6	78%	44%	-	Median PFS 16 mo	-	Neutropenia (19%), thrombocytopenia (26%), PNP ≥3 (18%), fatigue (11%), myalgia (11%), infections (48%)
Treon et al,[34] 2007	27	B	6	85	48%	0% (CR)	Median TTP 7 mo	-	Neutropenia (14%), thrombocytopenia (7%), PNP (22%), dizziness (11%)
Ghobrial et al,[36] 2010	37	BR	6	88%	66%	8%	Median PFS 16 mo	96% at 1 y	Neutropenia (12%), Thrombocytopenia (8%), Anemia (8%), PNP (0%)
Leblond et al,[35] 2017	34	BD	6	75%	43%	4%	Median PFS 15 mo	84% at 2 y	Thrombocytopenia (35%), anemia (29%), and neutropenia (15%)
Kersten et al,[48] 2022	59	IRD	8	71	85	15	PFS 54% at 2 y	88% at 2 y	Anemia (12%), thrombocytopenia (12%), neutropenia (21%)
Treon et al,[43] 2014	31 (3 R/R)	CaRD	6–14	87%	68%	35%	PFS 65% at 15 mo	-	Dexamethasone-related hyperglycemia (23%), carfilzomib-related hyperlipasemia (16%), and neutropenia (6.5%). PNP irrelevant
Vesole et al,[44] 2018	7	Ca		100%	86%	43%	Median PFS 19 mo	-	Cytopenia, neuropathy

Abbreviations: B, bortezomib; Ca, Carfilzomib; D, dexamethasone; HQR, high-quality responses (CR + VGPR); I, ixazomib; MRR, major response rate; ORR, overall response rate; OS, overll survival; PFS, progression-free survival; PNP, peripheral neuropathy; R, rituximab; WM, Waldentröm's macroglobulinemia.

The combination of everolimus, bortezomib, and rituximab was tested in 46 patients with RRWM.[40] Although the combination produced an ORR of 89% with a MRR of 53%, and the median PFS was 21 months, there were 63% treatment-related toxicities (fatigue, anemia, leucopenia, neutropenia, and/or diarrhea), which have put this regimen behind other better tolerable options.

There is a real-world experience with bortezomib-containing regimens in 32 patients with RRWM, including 10 (30%) who were refractory or intolerant to BTKi.[41] The ORR was 86%: CR 18%, VGPR 18%, PR 44%, and mR 4%. The 2-year OS and PFS was 90% and 76%, respectively. PNP (grade 1–2) occurred in 24% of patients but resulting only in 1 discontinuation. MRR was comparable between previously exposed or not to BTKi (84% vs. 75%, respectively).

Carfilzomib

Carfilzomib is another PI not only tolerable and active in monoclonal gammopathies, but also virtually free of neurotoxicity,[31] although this could be hampered by some cardiovascular problems.[42] The Dana–Farber group examined the combination of carfilzomib, rituximab, and dexamethasone (CaRD) in 31 symptomatic patients with WM, but only 3 of them had been previously treated with chemotherapy.[43] The ORR was 87% (1 CR, 10 VGPR, 10 PR, and 6 mR), and the PFS was 60% at 18 months. Most frequent toxicity was hyperglycemia, present in all patients at any grade (26% grade 3). PNP was notably reduced with respect to BDR (3%, grade 2), whereas cardiopathy, typically associated to carfilzomib, appeared only in 1 patient. There is an experience with CaRD in 7 patients with RR, with an ORR of 86%, 19 months of PFS, and a 14% of PNP/cardiopathy.[44]

Ixazomib

Ixazomib is an oral PI with limited neurotoxicity active and safe in MM.[45] These characteristics and its convenient once weekly oral administration has stimulated the use of ixazomib combined with dexamethasone and rituximab (IRD). This combination is useful in previously untreated patients with symptomatic WM,[46] so it has also been tested in RRWM. The Mayo Clinic presented the preliminary results of ixazomib plus ibrutinib for WM (NCT03506373),[47] in 21 patients: 9 newly diagnosed (ND)WM and 12 RRWM. The ORR was 76%, VGPRs 24%, PR 52%, mR 14%, and SD 10%, with no main differences between NDWM and RRWM. Although most patients developed AEs, very few were of grade 3–4: neutropenia (3 patients) and, anemia, hypertension, hypoxia, peripheral sensory neuropathy, and lung infection in 2 patients each.

The HOVON group carried out a trial in RRWM patients with IRD.[48] A total of 59 patients were enrolled with a median age of 69 years and a median of 2 prior treatments was 2 (range, 1–7). Response and survival were excellent (**Table 3**), and the toxicity was manageable: grade 2–3 cytopenias, grade 1–2 PNP, and grade 2–3 infections, demonstrating that the IRD regimen is efficient and tolerable.

Approved Bruton Tyrosine Kinase Inhibitors

B-cell receptor (BCR) signaling plays a central role in the survival support and growth of malignant B-cells in patients with B-cell lymphoproliferative disorders. This is especially relevant in WM, considering the major role of MYD88 mutation in the pathogenesis of WM. Accordingly, BTK currently represents a potent therapeutic target also in RR disease.[12,49] Its efficacy and use in clinical practice is rapidly changing the management of B-cell malignancies, including WM (see **Table 2**; **Table 4**).

Ibrutinib

Ibrutinib is the first-in-class inhibitor of BTK, displaying a unique targeted mechanism of action by inhibiting downstream signaling after interaction between the mutated

Table 3
Bruton tyrosine kinase inhibitors in Waldenström's macroglobulinemia

Study; 1st Author Ref	N	ORR %	CR + GVPR %	PR%	Median FU Time	Outcomes	Grade ≥3 Toxicity
Ibrutinib							
Treon et al,[15] 2015	63	91	30	49	59 mo	Median PFS: NR. 5-y PFS rate: 54%	Neutropenia 15%, thrombocytopenia 13%, CVE (grade 1–2) 15%, PNP 0%
Trotman et al,[52] 2021	31	87	29	48	58 mo	Median PFS: 39 mo. 60 mo PFS rate: 40%	Neutropenia 10%, thrombocytopenia 3%, CVE (grade 1–2) 16%, PNP 0%
Tam et al,[59] 2020	81	94	20	61	19 mo	Median PFS: NR. 18 mo PFS rate: 82%	Hypertension (11%), atrial fibrillation (4%), neutropenia (8%), anemia (5%), pneumonia (7%)
Ibrutinib + Rituximab							
Dimopoulos et al,[105] 2018	41	93	34	42	50 mo	Median PFS: NR. 54 mo PFS rate: 68%	Hypertension (13%), atrial fibrillation (12%), anemia (11%), and infusion-related reactions (1%)
Zanubrutinib							
Trotman et al,[52] 2021	53	94	51	29	36 mo	Median PFS: NR 36 mo PFS rate; 76.2%	CVE (grade 1–2) 6%, infection 3%
An et al,[58] 2021	43	77	33	37	33 mo	Median PFS: NR 24 mo PFS rate: 60.5%	CVE (grade 1–2) 6%, infection 3%
Tam et al,[59] 2020	83	94	29	49	19 mo	Median PFS: NR 18 mo PFS rate: 86%	Hypertension (6%), atrial fibrillation (0%), neutropenia (20%), anemia (5%), pneumonia (1%)
Acalabrutinib							
Owen et al,[62] 2020	92	95	27	57	63.7 mo	Median PFS: 67.5 mo 66 mo PFS rate: 52%	CVE (grade 1–2) 6%, infection 3%
Tirabrutinib							
Sekiguchi et al,[64] 2022	9	89	33	56	25 mo	Median PFS: NR 24 mo PFS rate: 88.9%	Neutropenia (22%), lymphopenia (19%), and leukopenia (11%)
Orelabrutinib							
Cao et al,[65] 2022	9	89	21.3	60	16 mo	Median PFS NR: 12 mo	Neutropenia (10.6%), leukocytopenia (6.4%), thrombocytopenia (6.4%), and pneumonia (4.3%)

Abbreviations: CVE, cardiovascular events; HQR, high-quality responses (CR + VGPR); NR, not reached; ORR, overall response rate; PFS, progression-free survival; PNP, peripheral neuropathy; PR, partial response; WM, Waldenström macroglobulinemia.

Table 4
Selected adverse events reported in clinical trials with BTK inhibitors in patients with Waldenström's macroglobulinemia

	Ibrutinib Treon et al,[15] 2015	Ibrutinib Tam et al,[59] 2020	Ibrutinib R Buske et al,[54] 2020	Zanubrutinib Trotman et al,[52] 2021	Zanubrutinib Tam et al,[59] 2020	Acalabrutinib Owen et al,[62] 2020	Tirabrutinib Seghiguki et al,[64] 2022	Orelabrutinib Cao et al,[65] 2022
FU	59 mo	44 mo	50 mo	36 mo	44 mo	63.7 mo	24.8 mo	16.4 mo
AE leading to drug discontinuation %	7.9	20.4	11	13	8.9	16	0	6.4
AE leading to dose reduction %	19	26.5	22.6	NR	15.8	NR	NR	NR
Hematological toxicity								
Neutropenia grade 3/4%	15.8	10.2	13	15.6	23.8	17	44	10.6
Anemia grade 3/4%	1.6	6.1	12	-	11.9	6	0	0
Thrombocytopenia grade 3/4%	11.1	6.1	1	9.1	10.9	NR	0	6.5
Infection grade 3/4%	6.3	27.6	29	27.3	21.8	33	0	8.5
Pneumonia grade 3/4%	3.1	10.2	11	3.9	1	9	0	4.3
Atrial fibrillation any grade %	12.7	23.5	19	-	7.9	12	11	0
Hypertension grade 3/4%	0	20.4	15	3.9	8.9	4	0	0
Bleeding grade 3/4%	NR	10.2	7	3.8	8.9	7	0	2.1
Diarrhea grade 3/4%	0	2	NR	2.6	3	NR	0	0

Abbreviations: AE, adverse event; BTK, Bruton tyrosine kinase; NR, not reached; WM, Waldentröm macroglobulinemia.

MYD88 protein and BTK. It was approved by the FDA in 2015 for symptomatic WM[50] based on the results of an investigator-initiated multicenter phase II study in 63 symptomatic previously treated patients in whom ibrutinib exerted a rapid increase in hemoglobin levels and rapid decreases in serum IgM.[15] At the extended follow-up of 59 months, in a population of heavily pretreated patients (median 2 prior lines, 40% refractory), ibrutinib monotherapy induced an ORR of 91%, an MRR of 71%, and 30% VGPR. Importantly, the 5-year PFS rate was 54%. Treatment with 3 or more versus 1 to 2 prior lines of therapy significantly impacted PFS duration (5-year PFS rate, 38% vs. 68%; $P = .01$), suggesting the preferred early use of ibrutinib in case of progression in BTKi-naïve patients.[51] *CXCR4*^{mut} cases, compared with *CXCR4*^{WT}, had a lower MRR (68% vs. 97%), and VGPR (47% vs. 9%), as well as longer median time to MRR (4.7 vs. 1.8 months). No MRs were observed in the 4 *MYD88*^{WT} patients. PFS was not reached in patients with *MYD88*^{mut}/*CXCR4*^{WT}, 4.5 years for *MYD88*^{mut}/*CXCR4*^{mut}, and 4 months for *MYD88*^{WT} patients.

Ibrutinib is effective even in the setting of rituximab refractory patients. In the arm C of the phase III iNNOVATE trial, the BTKi given as a single agent in 31 rituximab refractory and heavily pretreated patients attained a high ORR (87%) including 29% VGPR, with a median PFS of 39 months.[16] As in the pivotal trial, PFS was better for *MYD88*^{mut}/*CXCR4*^{WT} versus 18 months in *MYD88*^{mut}/*CXCR4*^{mut}.[52]

In the multicenter iNNOVATE study,[53,54] patients with WM, mostly RR, were randomized to receive ibrutinib in combination with rituximab (IR) versus placebo-rituximab. IR demonstrated robust responses close to 80% or above that were consistent across all *MYD88* and *CXCR4* genotype subsets, suggesting that the combination can potentially overcome the relatively low responses seen with ibrutinib single-agent treatment in unfavorable genotypes. In RRWM, the 54-month PFS rate was 68% with IR versus 20% with placebo-rituximab and the PFS benefit was seen regardless of *MYD88* and *CXCR4* mutation status.

Some studies have evaluated ibrutinib in common clinical practice. In a series of 54 patients with RRWM,[55] the response raters (ORR and MRR) were consistent with those reported in clinical trials (ORR 89% with 78% MRR) and the discontinuation rate (21%).[15] There is also a comparison between patients treated with ibrutinib monotherapy on and off clinical trials.[56] The rate and depth of responses of 157 patients treated in common practice were comparable to that of patients on clinical trials. No significant difference was observed in the 4-year PFS of 72% versus 63% between ON and OFF trial patients, respectively ($P = .14$).

Zanubrutinib

Zanubrutinib was developed to maximize BTK inhibition and avoid off-target effects. In the first trial (phase I/II) evaluating the role of zanubrutinib in WM, there were 53 patients with RRWM.[57] ORR after 36 months of follow-up was high (94%), and MR was seen in 80% patients with RR with a median time to response of 2.8 months. A total of 39% achieved a VGPR at 12 months, and 51% at 24 months. Similar results with a favorable VGPR or better (33%) and response benefit independent from genotype were observed in the phase II Chinese study after a median follow-up of 33 months.[58]

The ASPEN trial is a head-to-head study comparing ibrutinib with zanubrutinib with the primary endpoint of achieving better CRs plus VGPRs in patients receiving the new BTKi.[59] *MYD88*^{MUT} patients were randomized to receive 1 of the 2 inhibitors, whereas those with *MYD88*^{WT} received directly zanubrutinib.[53] Most patients enrolled in cohort 1 had RR disease. The primary objective was not met (28% with zanubrutinib vs. 19% with ibrutinib $P = .09$). There was no difference in ORR with zanubrutinib

compared to ibrutinib (94% vs. 93%, respectively), or in MRR (77% vs. 78%) or 18 months PFS (84% vs. 85%). Median time to achieve at least a VGPR was shorter for zanubrutinib (7 months) compared to ibrutinib (17 months).[60] PFS rate at 42 months was not significantly different. A longer follow-up has demonstrated that patients carrying *CXCR4*^{MUT} achieved a deeper response with zanubrutinib (21% vs. 10%), faster responses, and better PFS (42 months PFS rate: 73% vs. 42%).

In patients without *MYD88* mutation of the cohort 2 of the ASPEN trial, zanubrutinib led to a 65% MRR, with 31% VGPRs and CRs. At 42 months, PFS was 52%. In 2021, zanubrutinib was approved by the FDA and EMA for patients with WM.[53,60]

A phase II expanded access study with zanubrutinib enrolled 50 patients in the United States,[61] and 33 patients with RRWM treated with a median of 2 prior lines. The median duration exposure was 10 months, with 90% of patients achieving a response with a high rate of VGPR (43%). The favorable toxicity profile was confirmed.

Nonapproved Covalent Bruton Tyrosine Kinase Inhibitors

Acalabrutinib

The second-generation BTKi acalabrutinib (ACP-196) was developed to be more potent and selective than ibrutinib. In WM it was evaluated in monotherapy in a series of 108 patients, 92 of them were RRWM.[62,63] After 64 months of median drug exposure, ORR and MRR were 95% and 84%, respectively, with 4% of patients reaching a CR and 23% a VGPR according to the sixth IWWM response criteria. ORR was consistent across prespecified subgroups (age, IgM level, prior lines of therapy, ECOG). In this study, we do not have data on the impact of genotype as the *CXCR4* mutational status was not analyzed. The median duration of response and PFS was reached at 64.7 and 67.5 months, respectively. Up to now, acalabrutinib has not been approved by the regulatory agencies and no direct comparison of acalabrutinib with the other BTKi is available in patients with WM.

Tirabrutinib

Tirabrutinib was evaluated in 27 patients in a phase II monotherapy study at a daily dose of 480 mg in both treatment naïve and RRWM. Tirabrutinib exerted high response rates (ORR 96%) with rates of MRR similar in both patients with TN and R/R (89% in both), time to overall and MR was of 1 and 2 months, respectively. Of the 9, 3 patients with RR reached a good quality of response. At the 2-year follow-up, only 2 patients had discontinued treatment due to disease progression.[64] In August 2020, tirabrutinib was approved in Japan for patients with TN or R/R WM and LPL.

Orelabrutinib

Orelabrutinib is a novel, small molecule, selective irreversible BTKi investigated in a multicenter phase II trial in 47 patients with R/R. After a median time to response of 1.9 months, 89% of patients reached a response, with 21% achieving at least a VGPR. The follow-up of the study is still short. The estimated 12-month PFS is 89%.[65]

Noncovalent Bruton tyrosine kinase inhibitors

Pirtobrutinib. Pirtobrutinib is a highly selective, noncovalent (reversible) BTKi with promising efficacy in patients with RR B-cell malignancies.[66] The BRUIN study included 78 RRWM with a median age of 68 years and a median of 3 prior therapies.[67] A total of 85% patients had received chemoimmunotherapy alone, and 64% had received a BTKi (n = 61). Among the latter, 66% had discontinued prior BTKi due to disease progression. The MRR was 68%, including 24% VGPRs and 44% PRs. With a median follow-up of 8 months, the 6-month estimated duration of response (DoR) rate was 86%. In the BTKi-pretreated subset, the 6-month DoR was 83%.

Considering all B-cell malignancies treated with pirtobrutinib (n = 725), the most frequent AEs were fatigue (26%), diarrhea (22%), and contusion (19%). Neutropenia grade ≥3 was present in 20%, hypertension in 3%, hemorrhage in 2%, and atrial fibrillation/flutter in 1%. Overall, 2% of patients discontinued due to a treatment-related AE.[67]

Nemtabrutinib. Nemtabrutinib (MK-1026, formerly ARQ-531) is a noncovalent, potent inhibitor of both wild-type and ibrutinib-resistant C481S-mutated BTK,[68] the most common mechanism of resistance to covalent BTKis.[69] This drug was tested in 112 heavily pretreated patients with RR B-cell malignancies,[70] including 6 patients with WM. Responses were promising and toxicity manageable. No data are yet available for WM, but responses are possible, and data will be available from the NCT03162536 ongoing trial.

Bruton Tyrosine Kinase Inhibitors Adverse Events

BTKi treatment requires continuous administration for an indefinite course. Although treatment with BTKi is generally well tolerated and many early secondary effects usually decrease over time, prolonged drug exposure may translate into a progressively increased rate of AE. A major concern with continuous treatment is the development of AEs leading to intolerance and definitive treatment discontinuation, which translates into a poor prognosis. Ibrutinib's abrupt discontinuations to manage AE may be associated with a quick increase of IgM and potential withdrawal symptoms such as fever, body aches, headache, and arthralgias.[71]

Table 4 reports the definitive discontinuations and dosage reduction rates due to AE seen in large clinical trials. It is difficult to compare the tolerability of the BTKi as studies have different observation periods and characteristics of enrolled patients. The only study allowing a direct head-to-head comparison of AEs with ibrutinib and zanubrutinib is the ASPEN randomized trial.

Ibrutinib exerts the highest off-target effects. Patients often see atrial fibrillation, hypertension, hemorrhages, diarrhea, arthralgia, and rash, although most episodes are limited to grade 1–2.[72] Ventricular arrhythmias are uncommon, but they are the most worrisome toxicity of ibrutinib, and have also been reported with acalabrutinib.[73] Risk factors associated with atrial fibrillation are advanced age, prior history of cardiopathies, and hypertension, which the BTKi may induce. Next-generation BTKi have minimized off-target toxicities, so they have less AEs and better tolerability. Although atrial fibrillation and hypertension have also been reported with acalabrutinib and zanubrutinib, these AEs were more frequent with ibrutinib.[62,74]

Other frequent grade ≥3 AE with BTKis are cytopenias, specifically neutropenia (range 10%–24%). Grade 3–4 infections are highly interesting in WM, and they are frequent, particularly during the early treatment period, especially upper respiratory tract infections and pneumonia.[51,62,74]

The limited number of patients treated with tirabrutinib and orelabrutunib does not allow drawing any conclusion, although atrial fibrillation and hypertension have been observed in a low frequency.[64,65]

The direct comparison of zanubrutinib with ibrutinib showed that the former was better tolerated and associated with a lower risk of AEs leading to dose reductions (16% vs. 27%), treatment discontinuation (9% vs. 20%), or death (3% vs. 5%). Several AEs were statistically more frequent with ibrutinib than with zanubrutinib, including atrial fibrillation, hypertension, diarrhea, peripheral edema, muscle spasms, and pneumonia ($P < .05$ for all comparisons). In contrast, neutropenia occurred more frequently with zanubrutinib ($P < .05$), although did not translate into more infections.[59]

Stem Cell Transplant

Stem cell transplantation (SCT) has been shown to produce durable responses with a treatment-related mortality rate of 3.8%, although virtually all data came from retrospective studies.[75] Good outcomes were seen with high-dose treatment; 5-year PFS and OS rates were 40% and 69%, respectively.[76] In total, 22% of patients achieved a CR after ASCT. Data on allogeneic SCT are also derived from retrospective studies only. A retrospective series of 144 patients with WM demonstrated an OS of 74% after 1 year and 52% after 5 years, with PFS of 68% and 46%, respectively. The 1- and 5-year nonrelapse mortality was 15% and 30%, respectively.[77] SCT is less recommended in WM at present because of its high toxicity and the existence of more tolerable therapies.

OTHER EMERGING TREATMENTS

BCL2 Inhibitors

Venetoclax

BCL2 is an apoptosis inhibitor overexpressed in WM.[78] Venetoclax is a selective BCL2 inhibitor that is very effective in several hematological malignancies. In a phase II trial, 32 patients with RRWM received 200 to 800 mg venetoclax daily for 2 years, including 16 previously exposed to BTKis. The median FU was 33 months, and ORR and MRR were 84 and 81%, respectively. The median PFS was 30 months. MRR was lower in refractory versus relapsed patients (50% vs. 95%; $P = .007$). Neutropenia was the only occurring grade $\geq$3 AE (45%), including 1 episode of febrile neutropenia. No tumor lysis syndrome was observed, except one case with abnormal laboratory findings. Grade 2 AEs were seen in most patients (94%), mostly anemia, lymphopenia, and neutropenia. Temporary drug hold occurred in 14 patients, usually due to neutropenia, infections, or diarrhea. A phase II trial assessing the combination of venetoclax with ibrutinib in NDWM was done, with interesting results, but with an excess of ventricular arrhythmia, including 2 sudden deaths, which caused a full clinical hold on this trial.[79]

Phosphatidylinositol 3-Kinase Inhibitors

Phosphatidylinositol 3-kinase inhibitors have provided good results in indolent B-cell lymphoproliferative disorders,[80] so they are interesting for WM. Idelalisib, one of the most popular ones, combined with obinutuzumab demonstrated an ORR of 71% and a median PFS of 25 months,.[81] Still, no further development has been pursued due to excess toxicity.[81,82]

Antibodies

Anti-CXCR4 monoclonal antibodies

CXCR4 mutations are present in 30% to 40% of patients with WM.[1] They can impact the clinical and biological behavior of patient with WM.[83] Thus, targeting CXCR4 in WM has been assessed in clinical trials. Ulocuplumab is a CXCR4 antagonist evaluated with ibrutinib in 13 patients with WM (4 RR) in whom the CXCR4 had been demonstrated.[84] This combination resulted in an MRR of 100% with a predicted 2-year PFS of 90%, but the drug development has been stopped. Another CXCR4 antagonist, mavorixafor, has been tested with ibrutinib in 9 patients with WM with *MYD88* and *CXCR4*^{WHIM}, providing a 100% ORR with only 9 AEs (79% grade 1) attributed to mavorixafor, and just two grade 2 AEs leading to discontinuation.[85]

Anti-PD1 antibodies

PD-1 has been implicated in T-cell regulatory function in the WM microenvironment.[86] Actually, PD-1 is expressed on B-cells in WM, promoting malignant cell viability

and proliferation.[87] There is, therefore, a rationale to investigate the efficacy of PD-1 blockade in WM.

The UK group developed the PEMBROWM trial to determine the safety, tolerability, and efficacy of pembrolizumab in combination with rituximab in RRWM previously exposed to covalent BTKis (NCT03630042).[88] A total of 17 patients had been initially registered, with median age of 70 years, and the majority (n = 15) having received a BTKi as the last therapy. With a median follow-up of 15 months, the ORR after 24 weeks was 47%, with 6% attaining VGPR, 18% PR, 18% mR, and 6% with an unavailable response but with evidence of mR at week 12. The median PFS was 13 months, and the median OS was not reached. There were 3 discontinuations due to AE: immune thrombocytopenia (1), and infection (2, including one COVID-19 infection), but most AEs were grade 1–2. Accordingly, pembrolizumab demonstrated safety, tolerability, and potential efficacy combined with rituximab, which requires future trials to demonstrate its real efficacy in WM.

There is a small experience with atezolizumab (anti-PD-L1) in combination with anti-CD20 in patients with RRMCL (n = 30), WM (n = 4), or MZL (n = 21).[89] Although results were encouraging in MCL and MZL, no responses were seen in WM, so this strategy should be changed for the future.

Tislelizumab combined with zanubrutinib has been tested in RR B-cell malignancies (NCT02795182).[90] However, 2 patients with WM developed a direct antiglobulin test negative severe hemolytic anemia,[91] so WM was removed from the trial.

Anti-CD38

Expression of CD38, a marker of plasmacytoid differentiation, can be seen by immunohistochemistry in a subset of patients with WM.[92] Daratumumab, an anti-CD38 monoclonal antibody highly active in CD38+ plasma cell dyscrasias,[93] was tested in a phase 2 trial as monotherapy in 13 patients with RRWM. The trial yielded disappointing results, with an ORR of 23%, MRR of 15%, and median PFS of 2 months,[94] justified by the low intensity of CD38 expression in the surface of WM cells by flow cytometry.[95] Additional trials are ongoing, such as the NCT03679624 evaluating daratumumab combined with ibrutinib.

Anti-CD19

WM cells are positive for CD19 so this antigen could be the target for another directed therapy. Loncastuximab tesirine (ADCT-402) is an antibody-drug conjugate comprising anti-CD19 conjugated to a pyrrolobenzodiazepine dimer toxin. There is an experience with this compound in RR B-cell NHL (NCT02669017).[96] The trial demonstrated efficacy and tolerability, but only 1 patient with WM was recruited. A new trial with loncastuximab tesirine is under development led by the Boston group (NCT05190705).

T-cell Therapies

Chimeric antigen receptor (CAR) T-cell therapy is being introduced within the spectrum of all B-disorders.[97] CAR T therapy is highly efficacious in diffuse large B-cell lymphoma and acute lymphoblastic leukemia, and it is being accepted for mantle cell lymphoma[98] and CLL.[99] However, the experience is limited in WM. Only 3 very heavily treated patients with WM have been treated with CAR-T therapy.[100] This experience demonstrated that treatment was tolerated, and toxicities were consistent with those seen for CAR-T in other diseases. All 3 patients attained at least a clinical response, including 1 minimal residual disease-negative CR. A prospective trial for rare B-cell lymphoproliferative disorders will include around 60 patients with RRWM (NCT05537766).

Bispecific antibodies, another T-cell targeted immune therapy, are active in indolent NHLs, including WM.[101] In a phase I trial with a CD20xCD3 bispecific antibody in relapsed/refractory B-NHL including 3 RRWM, the most commonly reported grade 3 AEs were anemia, lymphopenia, infections, and neutropenia. Although the stimulating results in other diseases make bispecific antibodies a very attractive option in WM, they need more available data, making exploring them in prospective clinical trials urgent.

Other Therapies

Iopofosine I^{131} (CLR 131) is a targeted radiotherapeutic that has demonstrated efficacy in multiple myeloma,[102] although some efficacy has also been seen in WM (unpublished data). Accordingly, a phase II trial has been started to evaluate iopofosine in RRWM (NCT02952508).

WHICH THERAPY SHOULD WE CHOOSE?

Not all patients have to be treated. Pure biochemical relapses should not be treated, and a close monitorization should be used. If we face a patient with RRWM that requires treatment, the type of therapy must be individualized. Type of treatment should strictly depend on host and disease-related factors and prior therapy (**Fig. 1**).[12,49] The median response duration for the most frequent first-line therapies is 3, 5, and 6 years, for CDR, BDR, and Benda-R, respectively.[12,49] Accordingly, a longer response duration should suggest repeating the prior regimen. The most common limit used for such a decision is usually 3 years based on expert opinion,[49] but it will always depend on the treating hematologist. If the decision is the use of a different therapy, certain treatment attributes should be considered in the selection of salvage treatment such as duration (fixed duration vs. ongoing), potential toxicity, and the type of prior therapies, to select a different mechanism of action. Accordingly, if the patient has received chemoimmunotherapy as the first-line therapy, selecting a BTKi is the best option. If the first-line therapy was a BTKi, for the second line, we should select any of the combos with chemoimmunotherapy (see **Fig. 1**). In addition, the patient's age, comorbidities, and patient and physician preferences could further aid in selecting the best treatment

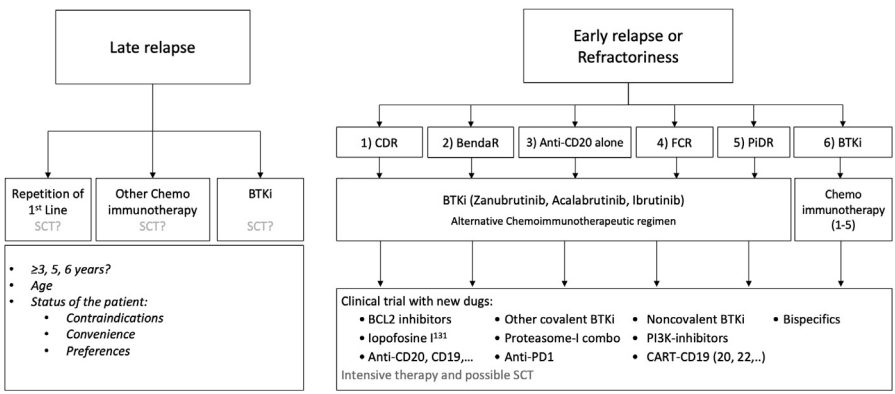

Fig. 1. Strategies at relapse: options of therapy. BendaR, bendamustine & rituximab; BTKi, Bruton tyrosine kinase inhibitor; CDR, cyclophosphamide, dexamethasone & rituximab; FCR, fludarabine, cyclophosphamide, rituximab; PiDR, proteasome inhibitor, dexamethasone and rituximab; RTX, rituximab; SCT, stem cell transplantation.

for a specific patient. For instance, patients with WM prefer fixed-duration treatment with the highest efficacy and the lowest risk of secondary malignancy.[103] Moreover, if the patient is young enough and does not harbor specific comorbidities, we must consider using an SCT, which always promises deep and long-term remissions.[75]

When selecting the therapy for a patient with WM, including salvage therapy, we recommend participating in clinical trials when possible. It could be the only possibility to access new drugs, which is especially relevant for patients who have already received chemoimmunotherapy and covalent BTKis.

CLINICS CARE POINTS

- If long-term PFS was achieved with initial therapy, the regimen can be repeated.
- If toxicity was a concern during first-line therapy, another approach should be made.
- If repeat initial therapy is not the option for your RRWM patient, after chemoimmunotherapy, use a BTK inhibitor; after BTKi failure, use chemoimmunotherapy.
- Pay attention to heart rate, blood pressure, bleeding, and absolute neutrophil counts when using BTK inhibitors.
- If your patient develops toxicity under BTKi therapy, stop for a short period until it is resolved and reinitiate at a lower dose.
- Pay attention to therapy interruptions during BTKi therapy; a relevant increase in the monoclonal protein can be seen (rebound phenomenon).

DISCLOSURE

No potential conflict of interest was reported by the author(s).

FUNDING

RGS received research funding and/or consulting fees from Novartis, Gilead, Astellas, Janssen, Amgen, Takeda, Janssen, Incyte, Astellas, BeiGene, AstraZeneca, Pfizer, and Pharmacyclics. AT declares being on the Advisory Board and Speaker Bureau for Janssen SPA, AbbVie, Astrazeneca, and Beigene.

CONFLICTS OF INTEREST

The authors declare that they have no potential conflicts of interest.

REFERENCES

1. Dogliotti I, Jiménez C, Varettoni M, et al. Diagnostics in Waldenström's macroglobulinemia: a consensus statement of the European Consortium for Waldenström's Macroglobulinemia. Leukemia 2022;37:388–95.
2. Campo E, Jaffe ES, Cook JR, et al. The international consensus classification of mature lymphoid neoplasms: a report from the clinical advisory committee. Blood; 2022.
3. Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World health organization classification of haematolymphoid tumours: lymphoid neoplasms. Leukemia 2022;36(7):1720–48.
4. Treon SP, Xu L, Yang G, et al. MYD88 L265P somatic mutation in waldenström's macroglobulinemia. N Engl J Med 2012;367(9):826–33.

5. Jimenez C, Sebastian E, Chillon M, et al. MYD88 L265P is a marker highly characteristic of, but not restricted to, Waldenstrom's macroglobulinemia. Leukemia 2013;27(8):1722–8.
6. Castillo JJ, Olszewski AJ, Kanan S, et al. Survival outcomes of secondary cancers in patients with Waldenström macroglobulinemia: an analysis of the SEER database. Am J Hematol 2015;90(8):696–701.
7. Garcia-Sanz R, Montoto S, Torrequebrada A, et al. Waldenstrom macroglobulinaemia: presenting features and outcome in a series with 217 cases. Br J Haematol 2001;115(3):575–82.
8. Kimby E, Treon SP, Anagnostopoulos A, et al. Update on recommendations for assessing response from the third international workshop on waldenstrom's macroglobulinemia. Clin Lymphoma Myeloma 2006;6(5):380–3.
9. Owen R, Kyle R, Stone M, et al. Response assessment in Waldenstrom macroglobulinaemia: update from the VIth International Workshop. Br J Haematol 2013;160(2):171–6.
10. Weber D, Treon SP, Emmanouilides C, et al. Uniform response criteria in Waldenstrom's macroglobulinemia: consensus panel recommendations from the Second International Workshop on Waldenstrom's Macroglobulinemia. Semin Oncol 2003;30(2):127–31.
11. Leblond V, Kastritis E, Advani R, et al. Treatment recommendations from the Eighth International Workshop on Waldenström's Macroglobulinemia. Blood 2016;128(10):1321–8.
12. Castillo JJ, Advani RH, Branagan AR, et al. Consensus treatment recommendations from the tenth International Workshop for Waldenström Macroglobulinaemia. Lancet Haematol 2020;7(11):e827–37.
13. Buske C, Sadullah S, Kastritis E, et al. Treatment and outcome patterns in European patients with Waldenström's macroglobulinaemia: a large, observational, retrospective chart review. Lancet Haematol 2018;5(7):e299–309.
14. Dimopoulos M, Kastritis E, Owen R, et al. Treatment recommendations for patients with Waldenstrom macroglobulinemia (WM) and related disorders: IWWM-7 consensus. Blood 2014;124(9):1404–11.
15. Treon SP, Tripsas CK, Meid K, et al. Ibrutinib in previously treated Waldenström's macroglobulinemia. N Engl J Med 2015;372(15):1430–40.
16. Dimopoulos MA, Trotman J, Tedeschi A, et al. 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):241–50.
17. Garcia-Sanz R, Ocio EM. Novel treatment regimens for Waldenstrom's macroglobulinemia. Expert Rev Hematol 2010;3(3):339–50.
18. Laszlo D, Andreola G, Rigacci L, et al. Rituximab and subcutaneous 2-chloro-2'-deoxyadenosine combination treatment for patients with Waldenstrom macroglobulinemia: clinical and biologic results of a phase II multicenter study. J Clin Oncol 2010;28(13):2233–8.
19. Leblond V, Lévy V, Maloisel F, et al. Multicenter, randomized comparative trial of fludarabine and the combination of cyclophosphamide-doxorubicin-prednisone in 92 patients with Waldenström macroglobulinemia in first relapse or with primary refractory disease. Blood 2001;98(9):2640–4.
20. Tedeschi A, Ricci F, Goldaniga MC, et al. Fludarabine, cyclophosphamide, and rituximab in salvage therapy of Waldenström's macroglobulinemia. Clin Lymphoma Myeloma Leuk 2013;13(2):231–4.

21. Souchet L, Levy V, Ouzegdouh M, et al. Efficacy and long-term toxicity of the rituximab-fludarabine-cyclophosphamide combination therapy in Waldenstrom's macroglobulinemia. Am J Hematol 2016;91(8):782–6.
22. Tedeschi A, Benevolo G, Varettoni M, et al. Fludarabine plus cyclophosphamide and rituximab in Waldenstrom macroglobulinemia: an effective but myelosuppressive regimen to be offered to patients with advanced disease. Cancer 2012;118(2):434–43.
23. Leleu X, Soumerai J, Roccaro A, et al. Increased incidence of transformation and myelodysplasia/acute leukemia in patients with waldenstrom macroglobulinemia treated with nucleoside analogs. J Clin Oncol 2009;27(2):250–5.
24. Leblond V, Tamburini J, Levy V, et al. Incidence of disease transformation and development of MDS/AML in 165 patients with waldenstrom's macroglobulinemia (WM) treated with fludarabine (F)-based regimen in three studies (French Cooperative Group on CLL/WM). ASH Annual Meeting Abstracts 2007;110(11):1291.
25. Paludo J, Abeykoon JP, Kumar S, et al. Dexamethasone, rituximab and cyclophosphamide for relapsed and/or refractory and treatment-naïve patients with Waldenstrom macroglobulinemia. Br J Haematol 2017;179(1):98–105.
26. Arulogun S, Brian D, Goradia H, et al. Bendamustine Plus Rituximab for the Treatment of Waldenström Macroglobulinaemia: Patient Outcomes and Impact of Bendamustine Dosing. Blood 2020;136(Supl.1):2.
27. 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):133–5.
28. 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):2637–42.
29. Paludo J, Abeykoon JP, Shreders A, et al. Bendamustine and rituximab (BR) versus dexamethasone, rituximab, and cyclophosphamide (DRC) in patients with Waldenström macroglobulinemia. Ann Hematol 2018;97(8):1417–25.
30. Olszewski AJ, Butera JN, Reagan JL, et al. Outcomes of bendamustine- or cyclophosphamide-based first-line chemotherapy in older patients with indolent B-cell lymphoma. Am J Hematol 2020;95(4):354–61.
31. Manasanch EE, Orlowski RZ. Proteasome inhibitors in cancer therapy. Nat Rev Clin Oncol 2017;14(7):417–33.
32. Dimopoulos MA, Anagnostopoulos A, Kyrtsonis MC, et al. Treatment of relapsed or refractory Waldenstrom's macroglobulinemia with bortezomib. Haematologica 2005;90(12):1655–8.
33. Strauss SJ, Maharaj L, Hoare S, et al. Bortezomib therapy in patients with relapsed or refractory lymphoma: potential correlation of in vitro sensitivity and tumor necrosis factor alpha response with clinical activity. J Clin Oncol 2006;24(13):2105–12.
34. Treon SP, Hunter ZR, Matous J, et al. Multicenter clinical trial of bortezomib in relapsed/refractory Waldenstrom's macroglobulinemia: results of WMCTG Trial 03-248. Clin Cancer Res 2007;13(11):3320–5.
35. Leblond V, Morel P, Dilhuidy MS, et al. A phase II Bayesian sequential clinical trial in advanced Waldenström macroglobulinemia patients treated with bortezomib: interest of addition of dexamethasone. Leuk Lymphoma 2017;58(11):2615–23.

36. 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):1422–8.
37. Treon SP, Ioakimidis L, Soumerai JD, et al. Primary therapy of waldenstrom macroglobulinemia with bortezomib, dexamethasone, and rituximab: WMCTG clinical trial 05-180. J Clin Oncol 2009;27(23):3830–5.
38. Dimopoulos MA, Garcia-Sanz R, Gavriatopoulou M, et al. Primary therapy of Waldenstrom macroglobulinemia (WM) with weekly bortezomib, low-dose dexamethasone, and rituximab (BDR): long-term results of a phase 2 study of the European Myeloma Network (EMN). Blood 2013;122(19):3276–82.
39. Gavriatopoulou M, Garcia-Sanz R, Kastritis E, et al. BDR in newly diagnosed patients with WM: final analysis of a phase 2 study after a minimum follow-up of 6 years. Blood 2017;129(4):456–9.
40. Ghobrial IM, Redd R, Armand P, et al. Phase I/II trial of everolimus in combination with bortezomib and rituximab (RVR) in relapsed/refractory Waldenstrom macroglobulinemia. Leukemia 2015;29(12):2338–46.
41. Khwaja J, Uppal E, Baker R, et al. Bortezomib-based therapy is effective and well tolerated in frontline and multiply pre-treated Waldenström macroglobulinaemia including BTKi failures: a real-world analysis. EJHaem 2022;3(4):1330–4.
42. Dimopoulos MA, Moreau P, Palumbo A, et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. Lancet Oncol 2016;17(1):27–38.
43. Treon SP, Tripsas CK, Meid K, et al. Carfilzomib, rituximab, and dexamethasone (CaRD) treatment offers a neuropathy-sparing approach for treating Waldenstrom's macroglobulinemia. Blood 2014;124(4):503–10.
44. Vesole DH, Richter J, Biran N, et al. Carfilzomib as salvage therapy in Waldenstrom macroglobulinemia: a case series. Leuk Lymphoma 2018;59(1):259–61.
45. Moreau P, Masszi T, Grzasko N, et al. Oral ixazomib, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med 2016;374(17):1621–34.
46. Castillo JJ, Meid K, Gustine J, et al. Prospective phase II Study of ixazomib, dexamethasone and rituximab in previously untreated patients with waldenström macroglobulinemia. Blood 2017;130(Suppl 1):1487.
47. Ailawadhi S, Parrondo RD, Laplant B, et al. Phase II study of ibrutinib in combination with ixazomib in patients with waldenström macroglobulinemia (WM). Blood 2022;140(Supplement 1):9331–2.
48. Kersten MJ, Amaador K, Minnema MC, et al. Combining ixazomib with subcutaneous rituximab and dexamethasone in relapsed or refractory waldenström's macroglobulinemia: final analysis of the phase I/II HOVON124/ECWM-R2 study. J Clin Oncol 2022;40(1):40–51.
49. Kastritis E, Leblond V, Dimopoulos MA, et al. Waldenström's macroglobulinaemia: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2019;30(5):860–2.
50. Raedler LA. Imbruvica (Ibrutinib): first drug approved for the treatment of patients with waldenström's macroglobulinemia. Am Health Drug Benefits 2016;9(Spec Feature):89–92.
51. Treon SP, Meid K, Gustine J, et al. Long-term follow-up of ibrutinib monotherapy in symptomatic, previously treated patients with waldenström macroglobulinemia. J Clin Oncol 2021;39(6):565–75.

52. 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 iNNOVATE ™ trial. Clin Cancer Res 2021;27(21):5793–800.
53. Dimopoulos M, Sanz RG, Lee HP, et al. Zanubrutinib for the treatment of MYD88 wild-type Waldenström macroglobulinemia: a substudy of the phase 3 ASPEN trial. Blood Adv 2020;4(23):6009–18.
54. Buske C, Tedeschi A, Trotman J, et al. Five-year follow-up of ibrutinib plus rituximab vs placebo plus rituximab for waldenstrom's macroglobulinemia: final analysis from the randomized phase 3 iNNOVATE (TM) study. Blood 2020; 136(Supplement 1):24–6.
55. Abeykoon JP, Zanwar S, Ansell SM, et al. Ibrutinib monotherapy outside of clinical trial setting in Waldenström macroglobulinaemia: practice patterns, toxicities and outcomes. Br J Haematol 2020;188(3):394–403.
56. Castillo JJ, Sarosiek SR, Gustine JN, et al. Response and survival predictors in a cohort of 319 patients with Waldenström macroglobulinemia treated with ibrutinib monotherapy. Blood Adv 2022;6(3):1015–24.
57. Trotman J, Opat S, Gottlieb D, et al. Zanubrutinib for the treatment of patients with Waldenström macroglobulinemia: 3 years of follow-up. Blood 2020; 136(18):2027–37.
58. An G, Zhou D, Cheng S, et al. A phase II trial of the Bruton tyrosine-kinase inhibitor zanubrutinib (BGB-3111) in patients with relapsed/refractory waldenström macroglobulinemia. Clin Cancer Res 2021;27(20):5492–501.
59. Tam CS, Opat S, D'Sa S, et al. A randomized phase 3 trial of zanubrutinib vs ibrutinib in symptomatic Waldenström macroglobulinemia: the ASPEN study. Blood 2020;136(18):2038–50.
60. Tam CSL, Garcia-Sanz R, Opat S, et al. ASPEN: Long-term follow-up results of a phase 3 randomized trial of zanubrutinib (ZANU) versus ibrutinib (IBR) in patients with Waldenstrom macroglobulinemia (WM). J Clin Oncol 2022;40(16): 7521.
61. Castillo JJ, Kingsley E, Narang M, et al. A phase 2 expanded access study of zanubrutinib (ZANU) in patients (pts) with Waldenström Macroglobulinemia (WM). J Clin Oncol 2022;40(16_suppl):e19522.
62. Owen RG, McCarthy H, Rule S, et al. Acalabrutinib monotherapy in patients with Waldenström macroglobulinemia: a single-arm, multicentre, phase 2 study. Lancet Haematol 2020;7(2):e112–21.
63. 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 2022;6(S3):1020–1.
64. Sekiguchi N, Rai S, Munakata W, et al. Two-year outcomes of tirabrutinib monotherapy in Waldenstrom's macroglobulinemia. Cancer Sci 2022;113(6):2085–96.
65. Cao X, Jin J, Fu C, et al. Evaluation of orelabrutinib monotherapy in patients with relapsed or refractory Waldenstrom's macroglobulinemia in a single-arm, multicenter, open-label, phase 2 study. Eclinicalmedicine 2022;52:101682.
66. Mato A, Shah N, Jurczak W, et al. Pirtobrutinib in relapsed or refractory B-cell malignancies (BRUIN): a phase 1/2 study. Lancet 2021;397(10277):892–901.
67. Palomba ML, Patel MR, Eyre TA, et al. Efficacy of pirtobrutinib, a highly selective, non-covalent (reversible) BTK inhibitor in relapsed/refractory waldenström macroglobulinemia: results from the phase 1/2 bruin study. Blood 2022; 140(Suppl.1):1.

68. Muhowski EM, Ravikrishnan J, Gordon B, et al. Preclinical evaluation of combination nemtabrutinib and venetoclax in chronic lymphocytic leukemia. J Hematol Oncol 2022;15(1):166.
69. Jiménez C, Chan GG, Xu L, et al. Genomic evolution of ibrutinib-resistant clones in Waldenström macroglobulinaemia. Br J Haematol 2020;189(6):1165–70.
70. Woyach JA, Flinn IW, Awan FT, et al. Efficacy and safety of nemtabrutinib, a wild-type and C481S-mutated Bruton tyrosine kinase inhibitor for B-cell malignancies: updated analysis of the open-label phase 1/2 dose-expansion bellwave-001 study. Blood 2022;140(Supplement 1):7004–6.
71. Gustine JN, Meid K, Dubeau T, et al. Ibrutinib discontinuation in Waldenström macroglobulinemia: etiologies, outcomes, and IgM rebound. Am J Hematol 2018;93(4):511–7.
72. Bond DA, Woyach JA. Targeting BTK in CLL: Beyond Ibrutinib. Curr Hematol Malig Rep 2019;14(3):197–205.
73. Bhat SA, Gambril J, Azali L, et al. Ventricular arrhythmias and sudden death events following acalabrutinib initiation. Blood 2022;140(20):2142–5.
74. Tam CS, Dimopoulos M, Garcia-Sanz R, et al. Pooled safety analysis of zanubrutinib monotherapy in patients with B-cell malignancies. Blood Adv 2022;6(4):1296–308.
75. Kyriakou C. High-dose therapy and hematopoietic stem cell transplantation in waldenström macroglobulinemia. Hematol Oncol Clin North Am 2018;32(5):865–74.
76. Kyriakou C, Canals C, Sibon D, et al. High-dose therapy and autologous stem-cell transplantation in Waldenstrom macroglobulinemia: the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. J Clin Oncol 2010;28(13):2227–32.
77. Kyriakou C, Canals C, Cornelissen JJ, et al. Allogeneic stem-cell transplantation in patients with Waldenström macroglobulinemia: report from the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. J Clin Oncol 2010;28(33):4926–34.
78. Chng WJ, Schop RF, Price-Troska T, et al. Gene-expression profiling of Waldenstrom macroglobulinemia reveals a phenotype more similar to chronic lymphocytic leukemia than multiple myeloma. Blood 2006;108(8):2755–63.
79. Castillo JJ, Sarosiek S, Branagan AR, et al. Ibrutinib and venetoclax in previously untreated waldenström macroglobulinemia. Blood 2022;140(Supplement 1):564–5.
80. Vanhaesebroeck B, Perry MWD, Brown JR, et al. PI3K inhibitors are finally coming of age. Nat Rev Drug Discov 2021;20(10):741–69.
81. Tomowiak C, Poulain S, Herbaux C, et al. Obinutuzumab and idelalisib in symptomatic patients with relapsed/refractory Waldenström macroglobulinemia. Blood Adv 2021;5(9):2438–46.
82. Castillo JJ, Gustine JN, Meid K, et al. Idelalisib in Waldenström macroglobulinemia: high incidence of hepatotoxicity. Leuk Lymphoma 2017;58(4):1002–4.
83. Roccaro AM, Sacco A, Jimenez C, et al. C1013G/CXCR4 acts as a driver mutation of tumor progression and modulator of drug resistance in lymphoplasmacytic lymphoma. Blood 2014;123(26):4120–31.
84. Treon SP, Meid K, Hunter ZR, et al. Phase 1 study of ibrutinib and the CXCR4 antagonist ulocuplumab in CXCR4-mutated Waldenström macroglobulinemia. Blood 2021;138(17):1535–9.
85. Treon SP, Buske C, Thomas SK, et al. Preliminary clinical response data from a phase 1b study of mavorixafor in combination with ibrutinib in patients with

waldenström's macroglobulinemia with MYD88 and CXCR4 mutations. Blood 2021;138(Supplement 1):1362.
86. Jalali S, Price-Troska T, Paludo J, et al. Soluble PD-1 ligands regulate T-cell function in Waldenstrom macroglobulinemia. Blood Adv 2018;2(15):1985–97.
87. Ansell SM. PD-1 Is expressed on B-Cells in waldenstrom macroglobulinemia and promotes malignant cell viability and proliferation. Blood 2014;124(21):3015.
88. Kothari J, Eyre TA, Rismani A, et al. Pembrowm: results of a multi-centre phase Ii trial investigating the safety and efficacy of rituximab and pembrolizumab in relapsed/refractory waldenström's macroglobulinaemia. Blood 2022;140(Supplement 1):3624–6.
89. Panayiotidis P, Tumyan G, Thieblemont C, et al. A phase-II study of atezolizumab in combination with obinutuzumab or rituximab for relapsed or refractory mantle cell or marginal zone lymphoma or Waldenström's macroglobulinemia. Leuk Lymphoma 2022;63(5):1–12.
90. Tam C, Cull G, Opat S, et al. An update on safety and preliminary efficacy of highly specific Bruton tyrosine kinase (BTK) Inhibitor zanubrutinib in combination with PD-1 inhibitor tislelizumab in patients with previously treated B-Cell lymphoid malignancies. Blood 2019;134:1594.
91. Othman J, Verner E, Tam C, et al. Severe hemolysis and transfusion reactions after treatment with BGB-3111 and PD-1 antibody for Waldenstrom macroglobulinemia. Haematologica 2018;103(5):E223–5.
92. Amaador K, Vos J, Pals S, et al. Discriminating between Waldenstrom macroglobulinemia and marginal zone lymphoma using logistic LASSO regression. Leuk Lymphoma 2022;63(5):1070–9.
93. Nooka AK, Kaufman JL, Hofmeister CC, et al. Daratumumab in multiple myeloma. Cancer 2019;125(14):2364–82.
94. Castillo JJ, Libby EN, Ansell SM, et al. Multicenter phase 2 study of daratumumab monotherapy in patients with previously treated Waldenström macroglobulinemia. Blood Adv 2020;4(20):5089–92.
95. Puig N, Ocio EM, Jiménez C, et al. Waldenström's Macroglobulinemia Immunophenotype. In: Leblond V, Treon S, Dimopoulos M, editors. Waldenström's macroglobulinemia. Cham: Springer; 2017. https://doi.org/10.1007/978-3-319-22584-5_2.
96. Hamadani M, Radford J, Carlo-Stella C, et al. Final results of a phase 1 study of loncastuximab tesirine in relapsed/refractory B-cell non-Hodgkin lymphoma. Blood 2021;137(19):2634–45.
97. Sterner RC, Sterner RM. CAR-T cell therapy: current limitations and potential strategies. Blood Cancer J 2021;11(4):69.
98. Tbakhi B, Reagan PM. Chimeric antigen receptor (CAR) T-cell treatment for mantle cell lymphoma (MCL). Ther Adv Hematol 2022;13. 20406207221080738.
99. Heyman BM, Tzachanis D, Kipps TJ. Recent advances in CAR T-Cell therapy for patients with chronic lymphocytic leukemia. Cancers 2022;14(7):1715.
100. Palomba ML, Qualls D, Monette S, et al. CD19-directed chimeric antigen receptor T cell therapy in Waldenström macroglobulinemia: a preclinical model and initial clinical experience. J Immunother Cancer 2022;10(2):e004128.
101. Bannerji R, Allan JN, Arnason JE, et al. Clinical activity of REGN1979, a bispecific human, Anti-CD20 x Anti-CD3 antibody, in patients with relapsed/refractory (R/R) B-cell non-hodgkin lymphoma (B-NHL). Blood 2019;134(Supplement_1):762.

102. Longcor J, Callander N, Oliver K, et al. Iopofosine I-131 treatment in late-line patients with relapsed/refractory multiple myeloma post anti-BCMA immunotherapy. Blood Cancer J 2022;12(9):130.
103. Amaador K, Nieuwkerk PT, Minnema MC, et al. Patient preferences regarding treatment options for Waldenström's macroglobulinemia: a discrete choice experiment. Cancer Med 2022;12(3):3376–86.
104. Chen CI, Kouroukis CT, White D, et al. Bortezomib is active in patients with untreated or relapsed Waldenstrom's macroglobulinemia: a phase II study of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 2007; 25(12):1570–5.
105. Dimopoulos M, Tedeschi A, Trotman J, et al. Phase 3 trial of ibrutinib plus rituximab in waldenstrom's macroglobulinemia. N Engl J Med 2018;378(25): 2399–410.