



Monoclonal antibody-based therapies for Waldenström's macroglobulinemia

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ABSTRACT

Monoclonal antibodies have established an important role in the treatment armamentarium of hematological malignancies, including Waldenström's macroglobulinemia. Rituximab, an anti-CD20 monoclonal antibody, is established as standard therapy for this unique low grade lymphoma, due to its effectiveness and safety as monotherapy, in combination with chemotherapy or other targeted therapies in WM. Newer monoclonal antibodies, targeting CD20 or other surface antigens, have shown to be effective in patients with WM. In the current review we attempt to provide an overview of the mechanisms of action of monoclonal antibodies and discuss clinical evidence that support their use in WM and their therapeutic potential.

1. Introduction

The recognition of cell surface differentiation antigens expressed in cancer cells led to the idea that antibodies could serve as targeted therapeutics [1]. Antibodies have two distinct functional domains, a constant fragment (Fc) that binds to effector cells through Fc γ receptors (Fc γ R) and a variable fragment that binds to a specific antigen. Monoclonal antibodies (MoAbs) usually have monovalent affinity and bind to a single epitope. They induce tumor cell killing via cytotoxic and immunomodulatory pathway activation which includes direct cellular apoptosis, antibody-dependent cellular cytotoxicity and phagocytosis (ADCC and ADCP) and complement-dependent cytotoxicity (CDC). Immune-mediated cytotoxicity (ADCC, ADCP, and CDC) requires interaction with the Fc γ R of effector cells (natural killer [NK] cells, cytotoxic T-cells, macrophages, granulocytes) [2]. The recruitment of C1q triggers the classical pathway of complement activation through C3b that has a dual role: it acts as opsonin and leads to the formation of the membrane attack complex that mediates CDC. Crosslinking of MoAb with the Fc γ R of macrophages and monocytes elicits ADCP. Direct cellular apoptosis occurs by blocking signal pathways necessary for proliferation and survival of cancer cells or activating apoptotic pathways [3]. MoAbs also modulate adaptive immune responses by Fc-dependent depletion of immunosuppressors cells and expansion of dendritic cells or effector T cells [4].

For over 20 years, anti-CD20 monoclonal antibodies have revolutionized the treatment of patients with B-cell lymphomas. They have shown efficacy as single agents and have improved response and survival rates when added to chemotherapy. Monoclonal antibodies are also safe and effective in patients with Waldenström's macroglobulinemia (WM) and have formed the backbone of most treatment combinations. WM is a rare, indolent B-cell lymphoma [5–7], characterized by the presence of a monoclonal IgM immunoglobulin in the serum and lymphoplasmacytic cell infiltration of the bone marrow/lymphatic tissue. [8] None of the available treatment combinations are currently officially approved for the disease by regulatory authorities. WM remains an orphan disease and an optimal therapeutic approach which allows for the induction of deep/durable responses and minimal toxicity remains to be established. New concepts for the use MoAbs have recently emerged: interference with tumor microenvironment, inhibition of angiogenesis, checkpoint blockade, delivery of cytotoxic drugs (antibody drug conjugates) and triggering of cytotoxic response by chimeric antigen receptor T cells and bispecific T cell engagers [3]. These concepts are gradually being integrated in the treatment approach of lymphomas including WM.

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2. Rituximab

2.1. Mechanism of action

Rituximab is a chimeric IgG1 monoclonal antibody (incorporating human immunoglobulin G1 heavy-chain sequences and murine immunoglobulin variable regions) which targets the CD20 surface antigen expressed on mature B-cells and in most non-Hodgkin's lymphomas B-cells, but not on early B-cell progenitors or later mature plasma cells [9]. It is the first approved monoclonal antibody in the field of onco-hematology. CD20 is part of a multimeric cell-surface complex that regulates calcium transport and is involved in the regulation of B-cell activation and proliferation [9]. CD20 is ubiquitously expressed on the lymphoplasmacytic clone that characterizes WM. Rituximab induces cell death by direct apoptosis, CDC and ADCC, while mechanisms like cytotoxic T cell generation and phagocytosis are also implicated [10].

Rituximab is currently approved by Food and Drug Administration (FDA) as a single agent or in combination therapy for the treatment of newly diagnosed or relapsed/refractory (R/R) low grade non-Hodgkin lymphoma (NHL), follicular lymphoma (FL), previously untreated diffuse large B-cell lymphoma and Chronic Lymphocytic Leukemia (CLL) and is widely used in patients with WM both in newly diagnosed and in the relapse setting.

2.2. Single agent rituximab

Rituximab monotherapy in WM has been evaluated in small retrospective and prospective series (Table 1). The first report was published in 1999 by Treon et al. In the E3A98 multicenter phase 2 trial four-weekly rituximab infusions were administered in 69 patients (34 treatment naïve and 35 R/R). The overall response rate (ORR) was 52.2%; major response was seen in 27.5% and minor response (MR) in 24.6%. The median duration of response was 27 months while previously untreated and pretreated patients seem to benefit equally [11]. In a prospective phase 2 study 27 patients with WM were treated with IV rituximab 375 mg/m² for four weeks, and 4 more weekly infusions at 3 months if there was no evidence of progression (termed as extended rituximab therapy); 44.0% achieved a partial response (PR) with a median time to response (TTR) of 3.3 months. One fourth of patients had mild infusion related reactions [12]. Among the 17 untreated WM patients, who received extended rituximab therapy 35.0% achieved a PR [median TTR 3 months, median time to progression 13 months] [13]. The impact of extended rituximab therapy on deepening response was also evaluated by Treon et al. (48.3% achieved a PR and 17.2% MR with median TTR of 17 months). Interestingly, the decline in serum IgM may continue even one year after the end of treatment with rituximab. Patients with lower serum IgM levels had significantly higher response rates [12]. An interesting observation is the paradoxical, rapid and transient rise in serum IgM levels (>25%), characterized as an "IgM flare", first described by Dimopoulos et al. [12], which was observed in up to 50% of patients following initiation of single agent rituximab and was occasionally associated with symptoms of hyperviscosity [14]. It was more common in patients with high serum IgM levels (> 4000 mg/dl). However, "IgM flare" does not constitute progression of the disease and patients should continue treatment and receive appropriate supportive management [15], with close follow-up to differentiate this

Table 1
Rituximab monotherapy studies in Waldenström's macroglobulinemia patients.

	N	ORR	MRR	PFS (months)
Dimopoulos et al. [12]	75	47%	32%	Not reported
Gertz et al. [11]	69	52%	28%	23
Treon et al. [47]	29	66%	48%	14

ORR: overall response rate, MRR: major response rate, PFS: progression free survival.

phenomenon from true disease progression or non-responsiveness. Strategies to avoid complications of "IgM flare" include pre-emptive plasmapheresis or induction therapy with non-antiCD20 monoclonal antibodies, especially in patients with IgM levels >4000 mg/dl¹⁵. Other common side effects of rituximab include are infusion-related reactions (IRRs) and late onset neutropenia (LON). [16] Infusion related reactions are commonly observed during the first infusion. These are usually mild to moderate, potentially threatening IRRs are seen in 10% of patients. Symptoms include rash, pyrexia, cough, vomiting, hypertension, dyspnea, angioedema and bronchospasm. The concurrent prophylactic administration of antihistamines and corticosteroids is currently considered standard practice. [17] LON is defined as an unexplained absolute neutrophil count of $\leq 1.5 \times 10^9/L$ occurring at least 4 weeks after the last rituximab treatment in patients (Grade 2–4). It has been reported up to 6–12 months after termination of rituximab. In most cases it is self-limited with no serious infectious complications.

A subcutaneous (SC) formulation of rituximab has been developed which is non-inferior to intravenous administration in terms of efficacy or pharmacokinetics, it saves considerable time and resources, and has comparable adverse events. Local skin reactions have been observed but are mild and self-limited. SC rituximab is approved for use for the treatment of CLL, DLBCL and FL in a fixed dose of 1400 mg. In WM patients, a phase I/II study evaluated the use of SC rituximab in combination with Ixazomib-dexamethasone. IRRs only occurred with the first IV infusion of rituximab and no IRRs or IgM flare was observed with SC rituximab [18]. Although not approved for WM, SC rituximab is commonly preferred over IV in the clinical practice and ongoing clinical trials are designed with rituximab in the SC formulation.

2.3. Rituximab combinations

The combination of rituximab with chemotherapy is the most widely used treatment for WM [15]. Table 2 summarizes clinical trials with rituximab-containing combinations in WM. The rationale is to combine MoAbs with regimens that have cytotoxic, cytostatic and immunogenic cell death activity, in order to optimize efficacy. Several studies have evaluated rituximab in combination with alkylators (bendamustine and cyclophosphamide) and nucleosides analogues (fludarabine and cladribine). These combinations achieve faster and deeper responses than single agent rituximab, with ORR between 80 and 95% and very good partial response (VGPR) rates between 25%–30%. However, there is also an increase of toxicity (myelosuppression, secondary malignancies, rash, infections). The combination of rituximab with proteasome inhibitors (PI) (bortezomib, carfilzomib and ixazomib) has also

Table 2
Rituximab combination studies in Waldenström's macroglobulinemia patients.

Combinations	N	ORR	MRR	Median PFS (months)
DRC [48]	72	83%	74%	35
R-CHOP	23	91%	NA	63
Rituximab-Fludarabine [49]	43	95.3%	86%	51
Rituximab-Cladribine [50]	29	89.6%	79%	Not reached (at 43 months follow-up)
Bendamustine-Rituximab [28]	257	92%	88%	65
Rituximab-Bortezomib-Dexamethasone [51]	59	85%	68%	43
Rituximab-Carfilzomib-Dexamethasone [52]	31	87.1%	68	46
Rituximab-Ixazomib-Dexamethasone [53]	26	96%	77%	40
Rituximab-Ibrutinib [23]	150	92%	72%	Not reached (at 30 months follow-up)

DRC: dexamethasone, rituximab, cyclophosphamide, R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, ORR: overall response rate, MRR: major response rate, PFS: progression free survival, NA: not available.

demonstrated efficacy, with ORR of 75%–95% and VGPR rates of 5%–35%, but there are concerns for worsening neuropathy particularly with the use of bortezomib. However, this combination may be preferred in patients with high IgM levels as the risk of IgM flare is reduced if induction with a PI is used, followed by the combination of the PI with rituximab. The unfavorable results and the increased toxicity observed with the use of immunomodulatory drugs (thalidomide and lenalidomide) in WM patients discourage this combination therapy with rituximab.

The discovery that the vast majority of WM patients harbor the somatic mutation *L265P* in *MYD88* gene [19] and the introduction of ibrutinib, a Bruton tyrosine kinase (BTK) inhibitor, has significantly changed the therapeutic landscape for WM patients. BTK is a non-receptor tyrosine kinase which plays a central role in B-cell signaling., [20] In WM, there is constitutive activation of BTK secondary to multiple mutations. The first mutation described, found in up to 90% of WM patients, is the somatic activating mutation of myeloid differentiation factor, *MYD88^{L265P} Leu265Pro*. [21] *MYD88^{L265P}* versus *MYD88^{WT}* patients have distinct clinical presentations and sensitivity to BTK inhibition. [22] Given its central role in the survival of the clonal WM cell, BTK and other molecules involved in the associated signaling pathways have become promising targets for the treatment of WM. The randomized phase 3 INNOVATE study showed that the addition of ibrutinib to rituximab substantially improves progression-free survival rates (82.0% vs 28.0%, HR: 0.20; $p < 0.001$) and higher rates of major responses (72.0% vs 32.0%, $p < 0.001$), both among treatment naïve and patients with relapsed or refractory disease [23]. The second-generation BTKi, zanubrutinib, was recently approved for WM based on the results of the phase III ASPEN trial. [24]

2.4. Rituximab maintenance

Complete response (CR) rates following induction therapy are <10% and most patients will eventually relapse. The possible long-lasting antitumor response to rituximab has prompted its role as maintenance therapy, similar to other low grade B-cell lymphomas.

Treon et al. reported a retrospective analysis of the outcomes of 248 patients who responded to rituximab-containing regimens and of which 35.0% subsequently received rituximab-maintenance (median maintenance infusions was 8 [range 1–40] over a 2-year period). Categorical responses improved in 41.8% of patients who received rituximab maintenance, versus 10.0% ($p < 0.001$) for those that did not receive maintenance. Patients who received rituximab maintenance achieved higher CR rates (16.3% vs 7.4%; $p = 0.05$), lower serum IgM ($p < 0.001$) and higher hematocrit levels ($p = 0.001$). Both PFS (56.0 vs 28.0 months, $p = 0.0001$) and OS (not reached vs 116.0 months, $p = 0.01$) were longer in the cohort of rituximab maintenance but a higher incident of respiratory tract infections (grade 2 or less) was observed [25].

Castillo et al. evaluated the role of rituximab maintenance in a retrospective study of 182 treatment-naïve WM patients who received induction therapy with rituximab-based regimens. Maintenance was administered as IV infusions every 2–3 months for up to 2 years and correlated with higher rates of major responses (97.0% vs 68.0%), better PFS (6.8 years vs 2.8 years) and better 5- and 10-year OS rates (95.0% and 84.0% vs 84.0% and 66.0%). In multivariate analysis, rituximab maintenance was associated with higher rates of deep responses (45.0% vs 29.0%, $p = 0.03$) and decreased risk of death [26]. In a retrospective study by Zanwar et al. in 2019, WM patients who received rituximab maintenance showed a trend to longer time to next treatment and significantly longer OS (not reached vs 10.1 years, $p = 0.02$) [27].

However, these positive observation from retrospective studies were not confirmed in a prospective, randomized, multicenter phase 3 study. The MAINTAIN study [28] failed to confirm the benefit of maintenance therapy in WM patients: the 2-year rituximab infusions (every 2 months) after induction with BR, improved PFS but the difference was not statistically significant compared to non-maintenance [Hazard ratio (HR)

0.8, $p = 0.3$], while there was no difference in OS. Thus, rituximab maintenance is not recommended for patients with WM that achieve at least PR after induction therapy.

2.5. Ofatumumab

Ofatumumab is a second generation fully human type I anti-CD20 monoclonal antibody that binds to a different epitope of CD20 than rituximab. [29] The binding epitope is located on the smaller extracellular loop of CD20 which is more membrane-proximal. ADCC activity is similar to rituximab but CDC activity is enhanced. Binding is more stable and the off-rate is slower. Cross-linking is required to induce apoptosis directly in a similar manner to rituximab. In vivo, ofatumumab induces B-cell depletion more efficiently than rituximab. It has exhibited potent CDC-mediated lysing activity against rituximab-resistant CLL cells with low CD-20 expression [30] and has also shown activity against cell lines with CD55 and CD59 expression which might be associated with rituximab resistance. [31] Compared to rituximab, cell lysis is induced at lower CD20 concentrations and the effects are more rapid. Ofatumumab is currently approved by the FDA and European Medicine's Agency (EMA) for patients with CLL.

2.6. Clinical trials

Prospective clinical trials have demonstrated the efficacy of ofatumumab in patients with WM, as a single agent, [32] in combination with fludarabine and cyclophosphamide [33] and in combination with bendamustine.

In a phase 2 prospective study, single-agent ofatumumab was administered to 37 patients; 24% of the patients were newly diagnosed and amongst previously treated patients 89% had prior exposure to rituximab. [32] Two dosing schedules were assessed; ofatumumab administered at 300 mg IV on week 1 and then at 1000 mg on weeks 2–4 for the first dosing schedule ($n = 15$) and 2000 mg IV on weeks 2–4 for the second schedule ($n = 22$). Ofatumumab was administered for 4 more weeks at the second dosing schedule to patients with stable disease or MR at 16 weeks ($n = 13$). ORR was 51.0% ($n = 19$) after cycle 1 and 59.0% ($n = 22$) after redosing. ORR was superior in newly diagnosed patients (67.0% vs 57.0%) and rituximab-naïve patients (75.0% vs 52.0%). Median TTR was 2.6 months and the PFS at 18 months was similar between the two groups. IgM flare was reported in two patients. The most common, low-grade adverse events were pruritus, urticaria, throat irritation and flushing. The rate of Grade 3–4 infusion reactions was 11.0% and other serious adverse events were hemolysis, neutropenia and chest pain (all seen in 5.0% of patients each).

A small phase 2 study evaluated the combination of fludarabine, cyclophosphamide, and ofatumumab (OFC) [33] in 12 patients with R/R WM. The median number of prior lines was one; 100% had prior rituximab exposure and 25.0% were refractory. IV Fludarabine and IV cyclophosphamide were administered on days 1–3 of four 28-day cycles. Ofatumumab 300 mg IV was administered on day 1 of cycle 1, 1000 mg IV on day 2 of cycle 1 and then 1000 mg on day 1 of cycles 3–4. Response distribution was 17.0% VGPR, 67.0% PR and 8.0% MR and 2-year median PFS was 80.0% and TTR 2.2 months. One Grade 2 infusion reaction was reported and 92.0% developed grade 3–4 neutropenia. There were no reports of IgM flare in this study.

The National Comprehensive Cancer Network guidelines include ofatumumab as an option for R/R WM patients as monotherapy or as combination-treatment and for rituximab intolerant individuals. In one study, among patients who were intolerant to rituximab and were exposed to ofatumumab, 82.0% achieved a response and tolerated the treatment. Ofatumumab intolerance has been reported in 20.0% of patients who are intolerant to rituximab. Ofatumumab is associated with a risk of IgM flare and therefore similar precautions need to be taken in patients with hyperviscosity or high IgM levels. Two prospective trials designed to assess the combination of bortezomib and ofatumumab in

the front line setting in WM patients (NCT01536067) and in the relapsed setting in low-grade B-NHL patients (NCT01119794) were terminated early due to lack of accrual and funding.

2.7. Obinutuzumab

Obinutuzumab is an Fc-engineered type II CD20 humanized monoclonal IgG1 antibody. In addition to an engineered variable region which allows type II antibody binding to CD20, Obinutuzumab is glycoengineered to bind with increased affinity to an activating Fc receptor, FcγRIII, which is expressed on immune effector cells like macrophages and NK cells.

In contrast to type I antibodies, type II antibodies do not mediate stabilization of CD20 in lipid rafts. They exhibit reduced binding to C1q and decreased CDC but induce direct cell death and ADCC more potently, mediated by cells displaying Fcγ receptors. ADCC activation seems to be stronger with Obinutuzumab compared to rituximab and ofatumumab as NK cells are recruited in a more efficient manner. [34] Rituximab, ofatumumab and obinutuzumab were compared in vivo in human lymphoma xenograft models; at doses of 30 mg/kg obinutuzumab induced complete tumor regression but the other two monoclonal antibodies failed to demonstrate the same activity at equivalent doses.

2.8. Clinical trials

Obinutuzumab is currently approved by FDA and EMA for the treatment of patients with CLL and advanced FL. In WM, the results of a prospective phase 2 study evaluating the combination of Obinutuzumab with idelalisib (a phosphoinositide 3-kinase inhibitor that blocks P110δ subunit) in patients with R/R WM were recently presented. The study enrolled 49 patients which received six cycles of continuous idelalisib at 150 mg twice daily with intravenous obinutuzumab as induction therapy and maintenance therapy with idelalisib alone for at least two years. Forty-eight patients were treated in the induction phase, and 27 patients received maintenance therapy. After a median follow up of 6.5 months, ORR was 71.4% and MRR 65.3%. The 12- and 24-month PFS rates were 75.5% and 55%, and the 12- and 24-month OS rates were 97.8% and 89.8%. No grade 5 adverse events were reported, but 26 patients discontinued treatment due to neutropenia (9.4%), diarrhea (8.6%) and liver toxicity (9.3%). [35] These toxicities were considered as mostly related to idelalisib; this may not be the optimal combination to evaluate the efficacy of obinutuzumab. Another multicenter, single-arm, phase II study of obinutuzumab induction followed by 2 years of maintenance in the R/R setting is also ongoing (NCT03679455) and recruiting patients.

Other anti-CD20 monoclonal antibodies [36], such as veltuzumab and ocrelizumab, are undergoing clinical development, but no WM-specific studies are planned with these agents.

2.9. Daratumumab

CD38 is a transmembrane glycoprotein which functions as a receptor, an adhesion molecule and an enzyme and is highly and uniformly expressed on plasma cells. Given that a significant proportion of the WM clone is lymphoplasmacytic, there is strong rationale for the development and use of anti-CD38 monoclonal antibodies. Daratumumab is a fully human IgG1k monoclonal antibody of CD38 highly and uniformly expressed on plasma cells. Preclinical studies demonstrated that daratumumab is a strong activator of CDC and ADCC in Multiple myeloma (MM)-derived cell lines and primary MM cells. It also induces potent ADCC in primary MM cells and xenograft mouse models even when CD38 expression is variable [37] and promotes helper T-cell and cytotoxic T-cell expansion and depletion of immunosuppressive CD38-expressing regulatory T-cells. [38] Daratumumab is currently approved by FDA/EMA for the treatment of MM and for systemic AL amyloidosis. [39]

A phase 2 study of IV daratumumab monotherapy (NCT03187262) in patients with R/R WM was terminated early because of futility ($n = 13$); treatment was stopped prematurely due to disease progression ($n = 9$) and lack of response ($n = 2$). Median PFS was 2 months. Grade 3/4 adverse events included neutropenia, thrombocytopenia, lymphopenia and others. [40] An ongoing phase 2 two-cohort study (NCT03679624) is evaluating the effectiveness of IV daratumumab plus ibrutinib in patients with WM. Cohort A includes ibrutinib-naïve patients and cohort B patients who have achieved less than a CR on single agent ibrutinib. The MM dosing schedule for daratumumab is followed and monthly continues up to cycle 25 at which point patients will continue on ibrutinib monotherapy until cycle 52. The estimated enrollment is 24 patients. Other anti-CD38 monoclonal antibodies are in clinical development but no WM specific clinical trials are currently planned.

2.10. Ulocuplumab

Ulocuplumab is a first-in-class, fully human IgG4 antibody that targets CXCR4 by preventing binding of its ligand CXCL12 to the receptor and therefore its subsequent activation. In preclinical studies ulocuplumab induces apoptosis of CLL cells at very low concentrations in the presence and absence of stromal cells in addition to CXCR4 activation. [41] It also exhibited significant MM cell cytotoxicity in a synergistic manner to bortezomib and inhibited adhesion of primary MM cells to the bone marrow.

Up to 40% of patients with WM harbor a somatic, usually subclonal, mutation in the CXCR4 gene (C-terminal of the C-X-X chemokine receptor type 4). [42] The same patient can harbor different CXCR4 mutations pointing to the presence of genomic instability. [43] SDF-1 is the CXCR4 ligand which stimulates CXCR4 to promote cell survival and proliferation. CXCR4 mutations promote constitutive activation of PI3K and ERK pathways due to a decrease of the internalization of CXCR4 providing a resistance mechanism to cell killing. [44] Clinically, symptomatic hyperviscosity and high levels of serum IgM are more frequent. Patients with CXCR4 mutations have a distinct clinical presentation with poorer responses to BTK inhibition, alkylators and PIs. [44, 45] Responses to ibrutinib in particular are less deep and less prolonged.

2.11. Clinical trials

Ulocuplumab is not currently FDA or EMA approved for the treatment of any condition. In a phase 1b study, in patients with R/R MM ($n = 44$) ulocuplumab demonstrated efficacy with an ORR of >50.0% when combined with lenalidomide and dexamethasone or bortezomib. [46]

There is an ongoing phase 1/2 study in WM patients who are both MYD88 and CXCR4 mutated. The study is currently not enrolling, initial accrual was planned at 38 participants but 13 patients have only been enrolled (NCT03225716). Planned dosing schedule for ulocuplumab was IV administration 2–4 times per cycle for cycles 1–6, at 3 dose levels in a 3 1 3 dose escalation fashion in phase 1 and with dose expansion in phase 2. Ibrutinib was given at 420 mg once daily PO (per os) as indicated.

LY2624587 is another fully humanized anti-CXCR4 antibody which inhibits SDF-1 binding to CXCR4, SDF-1-induced cell migration and CXCR4-ADF-1 mediated cell signaling via activation of MAPK and AKT pathways. It mediates receptor internalization and CXCR4 down-regulation on the cell surface. No WM specific studies are planned currently with LY2624587 or other anti-CXCR4 monoclonal antibodies.

3. Conclusions

Anti-CD20 monoclonal antibodies revolutionized the treatment of lymphomas, WM included. Since the introduction of rituximab more than two decades ago, monoclonal antibodies have been established as the backbone for treatment combinations for WM which include

chemotherapy and proteasome inhibitors. The combinatory effects of the above regimens have allowed improved response rates and better PFS. The therapeutic field in WM is currently moving towards the exploration of other membrane targets such as *CXCR4* and anti-CD38 and it remains to be seen which agent combinations will achieve the deepest and most prolonged treatment responses maintaining at the same time a safe toxicity profile. After the introduction of ibrutinib and other second generation BTK inhibitors, as well as bcl-2 inhibitors, the place of MoAbs in WM is challenged. However, MoAbs-based combinations still provide very active, fixed duration and cost effective therapy, with a well-known and manageable toxicity profile and in this regard it will be difficult to be substituted completely by small molecule-based therapy (BTK inhibitors or bcl-2 inhibitors). For WM it will be difficult to provide definitive guidance to the optimal primary therapy given that robust clinical data is limited and phase III randomized clinical trials hard to conduct given disease rarity and indolent course. Thus, MoAbs will continue, at least for the near future to be primary options for many patients with WM.

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