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Novel therapies for Waldenström Macroglobulinemia

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Abstract

Waldenström Macroglobulinemia (WM) is a rare hematologic malignancy characterized by the presence of lymphoplasmacytic lymphoma cells involving the bone marrow and production of a monoclonal IgM paraprotein. Recurrent somatic mutations in $MYD88^{L265P}$ and CXCR4 have been reported in 90-95% and 30-40% of patients with WM, respectively. Standard treatment regimens combine the anti-CD20 antibody rituximab with alkylating agents (e.g. bendamustine, cyclophosphamide), nucleoside analogs (e.g. fludarabine, cladribine), or proteasome inhibitors (e.g. bortezomib, carfilzomib, and ixazomib). Covalent BTK inhibitors (e.g. ibrutinib, acalabrutinib,

zanubrutinib) have shown to be safe and highly effective in patients with WM. Novel and promising agents in this disease include next-generation covalent BTK inhibitors (e.g. tirabrutinib, orelabrutinib), non-covalent BTK inhibitors (e.g. pirtobrutinib, ARQ531), BCL-2 antagonists (e,g. venetoclax), and CXCR4-targeted agents (e.g. mavorixafor, ulocuplumab), among others. Future studies will focus on developing fixed-duration combinations regimens with these novel agents aimed at increasing durable responses while minimizing toxicity and cost.

Keywords

Waldenström macroglobulinemia, Lymphoplasmacytic lymphoma, Bruton tyrosine kinase, BCL2, CXCR4

Introduction

Waldenström Macroglobulinemia (WM) is a rare hematologic malignancy defined by the presence of lymphoplasmacytic lymphoma (LPL) cells involving the bone marrow and production of a monoclonal IgM paraprotein. In addition, lymphoplasmacytic cells may involve lymph nodes, spleen, and extranodal sites.[1] WM can typically be monitored without treatment in asymptomatic patients. However, approximately 50% of patients may develop progression requiring treatment by 5 years and high-risk groups in under 2 years and require treatment.[2,3] Clinical manifestations frequently include anemia, constitutional symptoms, lymphadenopathy, splenomegaly as well as IgM-related syndromes such as hyperviscosity, peripheral neuropathy, cryoglobulinemia, cold agglutinin disease, and amyloidosis.[4-6]

WM Genomics

The most common mutations in WM are MYD88, CXCR4, ARID1A, and CD79B. 6q deletions associated with dysregulation of BTK, BCL2 and nuclear factor-*kappa* B (NF-kB) signaling are also frequently found.[7] The activating $MYD88^{L265P}$ mutation is found in 90% of cases of WM and in 60% of IgM monoclonal gammopathy of undetermined significance (MGUS).[8-9] $MYD88^{L265P}$ induces assembly of the "myddosome" which includes activated BTK and IRAK4/1 that results directly in downstream activation of NF-kB. $MYD88^{L265P}$ also upregulates transcription of HCK, which when transactivated by IL-6 triggers pro-survival signaling pathways via PI3K/AKT, MAPK/ERK1/2 as well as BTK. Finally, $MYD88^{L265P}$ interacts with the BCR pro-survival signaling pathway via LYN/SYK and STAT3.[7] Wild-type MYD88 ($MYD88^{WT}$) tumors may be driven by dysregulation of the NF-kB pathway through mutations in MALT1 and BCL10, DNA-repair mechanisms (mutations in TP53 or ATM) and epigenetics (mutations in histone methyltransferases or demethylators).[10] $MYD88^{WT}$ WM is characterized by a higher incidence of extramedullary involvement, a shorter time to progression until symptomatic WM, and a greater risk of transformation to high-grade lymphoma, which is associated with poor prognosis.[2,3,9,11] Acquired CXCR4 mutations ($CXCR4^{MUT}$) are present in up to 30-40% of WM patients, as well as 9% of IgM MGUS.[7,9] $CXCR4^{MUT}$ genotype consists of more than 30 different activating mutations, both frameshift and nonsense variants, which may lead to activation of the pro-survival factors AKT and ERK.[12] $CXCR4^{MUT}$ have been shown to be associated with significantly higher bone marrow disease infiltration, as well as higher serum IgM levels and incidence of hyperviscosity syndrome[13,74]. Of note, in contrast to $MYD88^{WT}$, $CXCR4^{MUT}$ disease is not associated with a worse prognosis.[13]

Standard Management Approaches

Most preferred frontline regimens according to NCCN guidelines entail rituximab-based combinations and include: bendamustine, rituximab (BR), bortezomib, dexamethasone, rituximab (BDR), and dexamethasone, rituximab, cyclophosphamide (DRC).[14] The best initial choice should be customized to the individual situation based on patient factors (i.e. fitness, baseline comorbidities, desire for fixed treatment duration), disease factors (i.e. disease bulk, presence of cytopenias, level of IgM) and mutational status (i.e. presence or absence of CXCR4 and MYD88 mutations)[15,16] In a retrospective comparison of fixed-duration therapies for treatment-naïve patients at Mayo Clinic, the regimen of BR was shown to have superior outcomes compared to that of DRC or BDR, leading to an overall response rate (ORR) of 98% and median progression-free survival (PFS) of 5.2 years. However, OS was not significantly different between the three cohorts. Interestingly, the status of $MYD88^{L265P}$ was not a predictive factor for outcomes in either of the three regimens.[17] In another retrospective study, treatment-naïve WM patients treated with BR, DRC and BDR had similar PFS and OS.[75] The presence of CXCR4 mutations do not seem to impact outcomes to chemotherapy or proteasome inhibitor-containing regimens.[18,19, 76]

FDA Approved BTK Inhibitors

Ibrutinib

In 2015, ibrutinib became the first drug FDA approved for treatment of WM. Ibrutinib is an orally administered, covalent BTK inhibitor (BTKi) shown to trigger apoptosis in WM cells with $MYD88^{L265P}$.[21] Long-term data was from the pivotal phase II trial of 63 patients with relapsed/refractory (R/R) disease with a median follow-up of 59 months showed a 5-yr PFS of 54%. Responses deepened over time with 30% of patients ultimately achieving a very good partial response (VGPR). However, patients who had $MYD88^{WT}$ or $CXCR4^{MUT}$ were found to have inferior PFS. Of the 4 patients with $MYD88^{WT}$, there were no major responses. Patients with $CXCR4^{MUT}$ (n=22) had a 68% major response rate (MRR) and experienced longer time to achieving a major response compared to those with $CXCR4^{WT}$ (n=36) (4.7 versus 1.8 months). This also translated into a significant difference in PFS between CXCR4 mutated and wild-type subgroups (5-yr PFS of 38% vs 70%). However, the median PFS is excellent among $CXCR4^{MUT}$ patients at 4.5 years.[21,22] Similar efficacy for ibrutinib was seen in 31 rituximab-refractory patients in a sub-study of the Phase III iNNOVATE trial. In this study, patients had failed to achieve at least a minor response or had relapsed within 12 months of receiving rituximab. A decreased efficacy of ibrutinib in $CXCR4^{MUT}$ patients was again seen in this patient population.[23,24] In the 4-year analysis of a phase II study of 30 treatment-naïve (TN) patients, there was an overall 4-yr PFS rate of 76% and a 100% ORR. In this study, the difference in PFS between $CXCR4^{MUT}$ mutated and $CXCR4^{WT}$ disease was less pronounced (4-yr PFS 59% vs 92%) and did not meet statistical significance, likely explained by the small sample size. No patients with $MYD88^{WT}$ were enrolled in this trial.[25,26] The addition of rituximab to ibrutinib (IR) was investigated in the phase III

iNNOVATE trial that compared rituximab plus ibrutinib with rituximab plus placebo in patients with treatment-naïve or R/R disease. Acknowledging the limitations of cross-trial comparisons, this combination does not appear to significantly improve depth or duration of response in MYD88^{L265P} CXCR4^{WT} disease compared to ibrutinib monotherapy. Of the 150 patients enrolled, ibrutinib and rituximab resulted in a 4-yr PFS rate of 70% in treatment-naïve patients and a major response rate of 76% in both treatment-naïve and R/R patients. Of note, 1 patient did achieve a complete response (CR) with the IR combination whereas no CRs were reported in the ibrutinib monotherapy trials. The median time to response was 1 month. There may be a potential advantage of IR versus ibrutinib monotherapy, as the combination of IR appeared to abrogate the inferior treatment response in CXCR4^{MUT} vs CXCR4^{WT} (MRR of 77% vs 81%) and resulted in a relative short time to major response at only 3 months, which compares favorably to the monotherapy trials (7.3 months in TN and 4.7 months in R/R). Finally, although numbers were small, 11 patients with MYD88^{WT} were enrolled in iNNOVATE with 73% achieving either a PR or VGPR, suggesting a role for IR combination in this small subset of patients.[27,28]

Zanubrutinib

Zanubrutinib is a novel, more selective covalent BTKi than ibrutinib.[29] A single-arm phase I/II trial investigating zanubrutinib in both TN and R/R patients with WM (n=77) demonstrated deep and durable responses with a VGPR rate of 45% and 3-yr PFS rate of 81%. The rate of VGPR was lower for CXCR4^{MUT} compared to CXCR4^{WT} cases (59%

vs 27%, respectively); however, the MRR was similar (91% vs 87% in $CXCR4^{whim}$ and $CXCR4^{WT}$, respectively). Furthermore, of the 8 patients who were $MYD88^{WT}$, all had at least a minor response (100% ORR) and 5 had a MRR (63%), including 1 CR. Among all subjects, responses deepened over time, with VGPR rates increasing from 21% at 6 months to 44% at 24 months.[29] Thus, zanubrutinib appears to induce responses in $MYD88^{WT}$ and $CXCR4^{MUT}$ disease. The open label, phase III randomized ASPEN trial was conducted comparing zanubrutinib to ibrutinib. In this study, 201 patients with either TN or R/R WM were 1:1 randomized to either agent. Patients with $MYD88^{WT}$ were enrolled in a third non-randomized cohort of zanubrutinib and analyzed separately. The primary endpoint was rate of VGPR or better at best response. Although there was a higher rate of VGPR for zanubrutinib versus ibrutinib (28% vs 19%), this was not statistically significant (p=0.09). The secondary endpoints also demonstrated similar efficacy between arms, including MRR (77 vs 78%) and 18-month PFS rate (85% vs 84%). Stratifying by CXCR4 mutational status also showed equivalent MRR rates between ibrutinib and zanubrutinib (63 vs 64%, respectively, in $CXCR4^{MUT}$). Interestingly, however, the median time to major response was longer for ibrutinib compared to zanubrutinib at 6.6 vs 3.1 months, respectively, in the $CXCR4^{MUT}$ patient subset.[30] In the ASPEN sub-study analyzing $MYD88^{WT}$ patients, 26 patients (21 R/R, 5 TN) were included for analysis. With a median of 18 months of follow-up, 50% achieved a major response, including 7 (27%) with a VGPR. As in the overall ASPEN cohort, the median time to major response was 2.9 months. The 18-month PFS rate was 68%.[31] Of note, in a separate trial of zanubrutinib conducted in R/R patients in China (n=44), 3/6

MYD88^{WT} patients achieved a major response (50% MRR), including 1 VGPR.[32] In September 2021, zanubrutinib was FDA-approved for patients with WM.

In conclusion, both FDA-approved BTKi are highly active in WM; however, zanubrutinib may be preferred over ibrutinib in MYD88^{WT} disease and when a short time to major response in CXCR4^{MUT} disease is desired.

Other covalent BTK Inhibitors

Acalabrutinib

Acalabrutinib is a 2nd generation highly selective, covalent BTK inhibitor administered at a dose 100 mg orally twice daily.[33] It was investigated in a dedicated phase II trial, which included 106 treatment-naïve and R/R WM patients. Acalabrutinib was highly active with response rates on par with ibrutinib. At a median follow-up of 27 months, the ORR was 93%. A major response was seen in 79% of those with TN disease and in 72% of those with R/R disease. Of the 50 patients with genotyping performed, the *MYD88^{L265P}* mutation was found in 36 patients (72%). The ORR was 94% in the 36 patients with *MYD88^{L265P}* disease, and 57% of the 14 patients with *MYD88^{WT}* disease. No patients with *MYD88^{WT}* disease attained a very good partial response (VGPR) or complete response (CR). With a median follow-up of 27 months, the 2-year PFS rate was 90% in treatment-naïve patients and 82% for R/R. Of note, 8/14 (57%) patients with MYD88^{WT} achieved a major response, whereas no major responses were reported in

the ibrutinib monotherapy trials. Unfortunately, CXCR4 status was not determined in this study and thus efficacy data in CXCR4 mutated cases not available.[33]

Tirabrutinib

Tirabrutinib (ONO/GS-4059) is a second-generation covalent BTK inhibitor with increased BTK selectivity and potency compared to ibrutinib. This drug was active across a range of B-cell malignancies, including 3 patients with WM, in a phase I first-in-human trial.[34] A dedicated phase II trial in enrolled 27 (18 TN and 9 R/R) WM patients in Japan, including 1 with $MYD88^{WT}$ and 4 with $CXCR4^{MUT}$ disease. The ORR was 96% and the MRR 89% with time to overall and major response 1 and 2 months, respectively. The median time to response was similar between $CXCR4^{WT}$ and $CXCR4^{MUT}$; however, the small number of patients with $CXCR4^{MUT}$ preclude drawing major conclusions. Tirabrutinib was equally effective in both TN and R/R cohorts (MRR of 89% in both).[35] After 2 years of median follow-up, the PFS rate was 94% and 89% in TN and R/R cohorts, respectively, with 100% OS in both. VGPR rate improved in both cohorts over time, increasing from 17% to 33% in TN patients and from 0% to 22% in R/R patients. One patient in the R/R cohort developed a CR. Currently, 22/27 patients remain on study drug with only 2 having discontinued due to disease progression.[36] Tirabrutinib was approved in Japan in August 2020 for patients with TN or R/R WM and LPL.

Orelabrutinib

Orelabrutinib is another novel highly selective covalent BTK inhibitor with significantly reduced off-target kinase inhibition. Preclinical studies demonstrate orelabrutinib lacks inhibition of ITK (IL-2-inducible T-cell kinase), which preserves the function of NK cell-mediated antibody-dependent cellular cytotoxicity (ADCC) as opposed to ibrutinib, in which ADCC is compromised.[37] Orelabrutinib is being investigated in a multicenter phase II trial in patients with R/R WM and early data were presented at ASH 2021. With 47 patients evaluable for analysis after 14 months of follow-up, the estimated 12-month PFS rate was 88%. MRR was 79%, with median time to response of 2 months. MRR was >50% in all high-risk subgroups (e.g., advanced age, anemia, thrombocytopenia, elevated B2M and serum IgM >7000) and 100% for the four patients who had 3 or more prior lines of therapy. One PR was attained out of the four patients that were $MYD88^{WT}$. VGPR rate was 15% and disease control rate was 98%. However, there were no CRs. Of note, $CXCR4^{MUT}$ was only detected in 4 patients (9%), as only $CXCR4^{S338X}$ mutations were investigated.[38]

BTK Inhibitor Toxicity

Although well tolerated, BTKis are associated with known off-target side effects. The most common grade ≥3 adverse events (AE) reported were cytopenias, specifically neutropenia (~10-20%), which seems to be equally problematic with ibrutinib, acalabrutinib and zanubrutinib. Thrombocytopenia was more frequently reported with ibrutinib than the second-generation BTK agents (10-20% vs. 5-10%). Severe cardiac

AEs, such as atrial fibrillation, hypertension, and ventricular arrhythmias are uncommon but the most worrisome of the toxicity profile of ibrutinib. There was a relatively high rate of atrial fibrillation in the pivotal ibrutinib trials (13% in R/R trial and at least 20% in TN trial). In contrast, the rate of atrial fibrillation with acalabrutinib was 5% and 2-5% with zanubrutinib. Although hypertension occurs with all agents, the occurrence of grade ≥3 events was reported at a substantially higher rate with ibrutinib (10-13%) compared to 2nd generation drugs (3-6%). Bleeding risk with 2nd generation drugs remains elevated, suggesting a greater role of BTK in driving platelet dysfunction. Contusion was observed in 29% patients on acalabrutinib and 33% on zanubrutinib, although there was only 1 patient with severe bleeding (epistaxis) in the acalabrutinib trial. In terms of infectious complications, upper respiratory tract infections (URI) are by far the most common type, generally occurring in >20% of all patients across trials. Infections are also frequently seen with 2nd generation agents. Acalabrutinib resulted in severe pneumonia in 5% of subjects and severe episodes of cellulitis (3%), urinary tract infection (2%), and sepsis (2%). 52% of patients on zanubrutinib developed an URI (all grade) and grade ≥3 cellulitis and pneumonia were reported in 5% and 4%, respectively. Other toxicities include gastrointestinal symptoms, joint and muscle pain, rash, and neurologic symptoms (i.e., headache and dizziness). Diarrhea was reported with ibrutinib in the iNNOVATE trial at 28-42% with up to 6% grade ≥3. However, a relatively high rate is also seen with both acalabrutinib and zanubrutinib (>20%), including grade ≥3 in 2-3% of patients. Arthralgias and myalgias are a common side effect of all BTKis, occurring at a rate of approximately 10-20%, but only a minority are severe. Rash was reported at a similar frequency across all agents (10-20%). Finally,

headache likely occurs more commonly with 2nd generation agents compared to ibrutinib. It was most frequent on acalabrutinib (39%) but also was reported at high rates on zanubrutinib (15-18% all grade).[22,23,26,27,29,30,33,] Safety data are significantly more limited for the newer BTKis. For tirabrutinib, grade ≥3 AEs were observed in 8 patients (30%), most prominently neutropenia (11%). There appears to be a relatively high incidence of stomatitis (15%) and rash (44%), which included 2 cases of grade ≥3. No cases of new atrial fibrillation were reported. No new safety signals were observed during the extended follow-up period.[35,36] Lastly, orelabrutinib was associated with grade ≥3 treatment-related AEs in 19% of subjects. The most common all grade AEs were cytopenias (28% thrombocytopenia, 19% neutropenia), URIs (13%), and rash (13%). Only one patient discontinued study drug due to AEs. There were no reported cases of atrial arrhythmias, although there was one case of sudden death on treatment of unknown cause.[38] In summary, given the variety of inter-trial methodology, patient population, and AE reporting, it is difficult to accurately compare toxicity profiles between BTK inhibitors. The one exception is the comparison of ibrutinib to zanubrutinib in the randomized ASPEN trial. These data report a lower rate of cardiac events (i.e. atrial fibrillation and hypertension), diarrhea, and bleeding with zanubrutinib versus ibrutinib. It also demonstrates that the incidence of infections is equivalent between agents despite a higher rate of neutropenia with zanubrutinib.[30]

BCL2 Inhibition with Venetoclax

Overexpression of the anti-apoptotic protein B-cell lymphoma/leukemia-2 (BCL2) has been implicated in tumorigenesis. As a regulator of mitochondrial apoptosis, BCL-2 binds to BH3 proteins, blocking activation of down-stream pro-apoptotic proteins BAX and BAK, thus inhibiting mitochondrial membrane permeabilization, release of cytochrome C and ultimately apoptosis.[39,40] Venetoclax was first investigated in a phase I study, which enrolled 106 patients with R/R non-Hodgkin lymphoma. Only 4 patients with WM were enrolled but all patients attained a PR with a median duration of response of 25 months.[41] In WM cells, *in* vitro and *ex vivo*, apoptosis was induced after treatment with venetoclax, and venetoclax sensitized WM cells to ibrutinib, indicating that upregulation of BCL2 may be an important mechanism of resistance to BTK inhibition.[42,43] A dedicated phase II trial investigating venetoclax monotherapy administered at doses of 800 mg orally daily for a maximum of 2 years was performed. For the first 6 patients enrolled, venetoclax was administered by slow dose ramp-up, beginning at 200 mg for 1 week, followed by 400 mg for 1 week, followed by 800 mg thereafter. Given the absence of tumor lysis syndrome, the remainder of the patients received venetoclax at an accelerated ramp-up schedule of 400 mg for one week before proceeding to 800 mg. Out of 32 evaluable patients, the median number of prior therapies was 2 (range 1-10) with 12 (38%) receiving ≥3 prior therapies and 11 (34%) being refractory to the last line of therapy. 16 (50%) were previously exposed to BTKis. All subjects were $MYD88^{L265P}$ and 17 (53%) had $CXCR4^{MUT}$. The ORR was 84% which included a MRR of 81% and VGPR rate of 19%. The ORR and the VGPR rate was higher in those that were BTKi naïve compared to those with prior BTKi exposure, though this difference was not significant. In contrast, there was a statistically significant

increase in time to major response in those with prior BTKi versus those that were naïve (4.5 vs 1.4 months). There was no difference in ORR based on CXCR4 mutational status. With a median follow-up of 33 months, 19 patients had progressed on therapy. The median PFS was 30 months. Interestingly, there was no significant difference in PFS between patients with prior BTKi exposure or BTKi-naïve patients or based on CXCR4 genotype. Of note, in the 10 patients who completed the 2-year treatment course and had extended follow-up, a rapid decline in PFS was seen between months 24 and 36, suggesting that fixed duration of venetoclax may be insufficient. In terms of safety, "laboratory" TLS was only observed in one patient and there were no cases of clinical TLS. The only frequently occurring grade ≥3 AE was neutropenia (45%), which resolved with G-CSF and only resulted in one case of febrile neutropenia. The most frequent grade ≥2 non-hematologic AEs were nausea (n=4), diarrhea (n=3), and URIs (n=3).[44] Based on the data from this trial, venetoclax was added to the NCCN guidelines as a treatment option for previously treated patients with WM.[14]

Future Directions and Approaches

There is a steadily growing field of effective agents to treat WM. As this disease is considered incurable, an important treatment paradigm is optimization of quality of life. This is most effectively pursued by achieving a balance between disease control and minimization of treatment toxicity and side effects. To continue advancing the field, investigation of novel drug classes and innovative trial designs are underway.

Targeting CXCR4

Patients with CXCR4^{MUT} have inferior response and PFS outcomes on BTKi. The negative prognostic impact also appears to be proportionate to degree of clonality, with levels >25% associated with lower rate of VGPRs as well as shorter PFS.[45]

Ulocuplumab

Ulocuplumab is a fully human anti-CXCR4 antibody that binds to the second extracellular loop of CXCR4. Derived from the IgG4 subclass, ulocuplumab does not induce complement or antibody-dependent cellular cytotoxicity upon engaging CXCR4, but merely blocks the CXCR4/CXCL12 interaction, hence abrogating cell survival signaling.[46,47] A phase Ib clinical trial investigating the combination of ulocuplumab and ibrutinib in WM was undertaken. Enrolled patients were BTKi-naïve and had MYD88^{L265P} and CXCR4^{MUT} disease. Ibrutinib was administered at 420 mg daily indefinitely and ulocuplumab was administered intravenously once weekly for cycle 1 and every other week for cycles 2-6 (28-day cycles). Ulocuplumab was dose-escalated between 400 mg to a maximum of 1600 mg depending on the cohort. Out of 13 enrolled patients, 9 were previously untreated, and 5 presented with symptomatic hyperviscosity. No unexpected toxicities were observed up to the highest dose cohort. Ibrutinib was dose-reduced in two patients and ulocuplumab given for all 6 cycles in 11 of 12 patients. Two subjects discontinued study drugs due to toxicity. Grade ≥3 AEs were uncommon and most notable for thrombocytopenia (n=4), hyperglycemia (n=2), and

supraventricular tachycardia (n=1). There were two occurrences of grade 4 thrombocytopenia and neutropenia. The most common low-grade AEs were fatigue, diarrhea, skin infection, rash, arthralgias, and cough. There were no notable infusion reactions with ulocuplumab. All patients achieved a major response and 33% a VGPR. The median time to major response was short at 1.2 months. With a median follow-up of 22 months, the estimated 2 yr-PFS rate was 90%. Despite encouraging data from this trial, no additional investigation in WM is planned as further development of ulocuplumab was terminated by the sponsor due to lack of meaningful clinical activity in other disease types.[48]

Mavorixafor

Germline gain-of-function mutations in the C-terminal domain of CXCR4 causes constitutive CXCR4/CXCL12 signaling and defective WBC trafficking, manifesting as the congenital WHIM syndrome (warts, hypogammaglobulinemia, infections, and myelokathexis). Mavorixafor is a highly selective oral small molecule allosteric inhibitor of CXCR4. In the first human study to treat WHIM syndrome, mavorixafor demonstrated a favorable toxicity profile, as well as proof-of-concept that this agent effectively restores WBC mobilization from the bone marrow.[49] In preclinical models with WM cells, the CXCR4 inhibitor plerixafor effectively blocked CXCR4 signaling inducing apoptosis. This agent also sensitized $CXCR4^{MUT}$ WM cells to ibrutinib.[50] Thus, a multicenter phase 1b trial investigating the safety and activity of the combination of mavorixafor and ibrutinib is underway. Eligible subjects must have confirmed $MYD88^{L265P}$ and $CXCR4^{MUT}$

disease. Both TN and R/R patients were included. Mavorixafor was administered orally once per day at escalating doses from 200 mg to 600 mg in combination of ibrutinib 420 mg daily. 16 patients were enrolled in this study with 14 evaluable patients at the time of data censoring in October 2021. 44% of subjects were treatment-naïve and 56% were previously treated. Four patients discontinued study treatment due to various side effects including musculoskeletal pain, fatigue, dysphagia. One patient developed severe sepsis resulting in death. One patient developed grade 3 atrial fibrillation as well as a cryptococcal infection but recovered and continued study drugs. All patients had decrease in IgM levels from a median of 4700 mg/dL to 770 mg/dL. Median hemoglobin increased by 3.8 g/dL over the first 12 months. Out of the 10 patients evaluable for efficacy analysis, 100% responded with 3 PRs and 1 VGPR.[51]

Non-covalent BTK inhibitors

Despite the remarkable efficacy of covalent BTK inhibitors in B-cell lymphomas, resistance to therapy ultimately develops related to the development of BTK mutations, such as BTK C481S, which is commonly seen in WM patients who have progressed on ibrutinib.[52] Pirtobrutinib (LOXO-305) is a non-covalent, reversible BTKi designed to attain maximal BTK inhibition throughout the dosing period regardless of BTK turnover.[53] The BRUIN trial was a phase I/II trial investigating pirtobrutinib in 323 patients with R/R B-cell malignancies, which established a RP2D of 200 mg PO once daily. Among 26 patients with WM who were enrolled, the median number of prior therapies was 3 (range 2-4) and 18 (69%) had previously been treated with a covalent

BTK inhibitor. Of those 18, 12 had progressed while on BTKi, while 6 had discontinued due to toxicity or other reasons. Out of the 26 patients with WM, ORR was 68%, with similar outcomes in patients with prior BTK inhibitor exposure. Of note, CXCR and MYD88 genotyping analysis has not yet been reported. The most frequent adverse events were fatigue (20%), diarrhea (17%) and contusion (13%). The incidence of grade ≥3 neutropenia was on par with other agents (10%); however, half of these were felt to be unrelated to drug. Infections, arthralgias, and rashes were notably less common than historically reported with BTKis. There were no cases of new cardiac arrhythmias.[53]

Combinations

To date, there has been limited data demonstrating superiority of multi-agent regimens over single agent, with the iNNOVATE trial of rituximab and ibrutinib vs rituximab being one notable exception. Buske and colleagues presented a randomized phase 2 trial at ASH in 2020 investigating the addition of bortezomib to dexamethasone, rituximab, cyclophosphamide (DRC) as first-line therapy for WM. In this large study, 204 patients were randomized to B-DRC or standard DRC. While this regimen induced a high rate of MRs (79%) and CR/VGPRs (19%) independent of MYD88 and CXCR4 mutation status, it did not meet the primary endpoint of improving PFS.[54] At ASH 2021, a phase 2 trial investigating the addition of bortezomib to bendamustine-rituximab (BRB) in patients at first relapse (after a rituximab-based regimen) was presented. The primary efficacy endpoint was to achieve an absolute increase in 18-month PFS from 50 to 65% to establish superiority compared to standard-of-care. Prior exposure to bortezomib or

bendamustine was allowed if there had been at least a partial response. Out of 38 evaluable patients the ORR was 82% and included 4 (11%) CRs and 15 (39%) VGPRs. The primary endpoint was met and at time of data censoring, the 30-month PFS was 79%. The combination was well tolerated without unexpected safety signals.[55] This study highlights that combining multiple active agents into a single regimen can lead to deep responses with a tolerable safety profile.

The combination of ibrutinib and venetoclax has been shown to have synergistic activity and be well-tolerated in CLL and mantle cell lymphoma. Moreover, given the impressive ability of this combination to induce deep responses, efforts are underway to determine the feasibility of fixed duration therapy, typically guided by MRD status.[56,57,58,59] To this end, trials are underway investigating the combination of venetoclax and ibrutinib in WM to be administered during a 2-year limited time frame. Examples include NCT04273139 (phase II for TN patients), and NCT04840602 (phase II randomized for TN patients comparing venetoclax + ibrutinib/rituximab versus ibrutinib/rituximab).

Fixed duration therapies

Historically, deeper responses seem to correlate with longer treatment-free intervals. However, there are limited data to validate depth of response after cessation of treatment as a surrogate endpoint for response duration, time to progression, or time until next treatment (TTNT). At ASCO 2021, a study was presented by Perera and colleagues that investigated the prognostic impact of depth of response on long-term outcomes in patients with WM treated with fixed duration chemoimmunotherapy. This

was an international, multicenter cohort study that included 319 patients with WM who were treated with frontline fixed duration regimens DRC, BR, and BDR. 256 patients were evaluable for the landmark analysis of patients who achieved a response at 6 months. With median follow-up of 63 months, the 5-yr PFS rates of subjects who achieved a major response at 6 months compared to those who did not was 71% vs 43%, respectively ($p<0.001$). In addition, the 5-yr TTNT was also significantly higher at 84% vs 54%, respectively ($p<0.001$). Finally, in a multivariable analysis controlling for other prognostic factors, major response at 6 months was independently associated with improvement in PFS, TTNT, and overall survival.[60] This study highlights the potential role of using major response at 6 months as a potential surrogate endpoint for future trials investigating fixed-duration therapies. However, it may be possible to extrapolate these data for the design of trials that use depth of response at any time point (potentially using MRD analysis) to guide timing of cessation of therapy. Currently, there are several ongoing trials exploring the feasibility of fixed duration therapy of non-chemotherapeutic agents, including BTK inhibitors. For example, the phase 2 ibrutinib-venetoclax trial investigates the combination of venetoclax and ibrutinib administered for a maximum of 2 years for patients with treatment-naïve disease [NCT04273139]. A randomized trial comparing venetoclax plus ibrutinib/rituximab to ibrutinib/rituximab also stops all therapy after 2 years [NCT04840602]. Finally, a randomized phase 2 trial investigating venetoclax/rituximab versus DRC stops venetoclax after only one year.

Other novel targets and pathways

Newly identified cell-signaling pathways and novel targets for WM are currently being investigated to further expand the treatment landscape for this disease. HCK, which activates BTK, ERK, and AKT can be inhibited by the oral tyrosine kinase inhibitor dasatinib, which is currently used for treating chronic myeloid leukemia. A phase I study of dasatinib in WM patients progressing on covalent BTK inhibitors in underway [NCT04115059]. Phospholipid-drug conjugates are a novel drug class, consisting of a phospholipid ether (PLE) conjugated to a cytotoxic warhead that is preferentially taken up by tumor cells. CLR-131 is a PLE conjugated to radioisotope iodine-131 that is administered intravenously and is currently being investigated in patients with R/R B cell malignancies (CLOVER-1). At ASCO 2021, early data were reported, which included 6 evaluable patients with WM. Impressively, 6/6 had a response to therapy, which included 1 CR and 4 PRs. 2 patients had $MYD88^{WT}$ disease and both had a major response including 1 CR.[61] Given its encouraging activity, a designated expansion cohort for WM patients with prior ibrutinib failure is currently underway, which plans to accrue 50 patients [NCT02952508]. Despite the rapidly evolving field of immunotherapy in cancer, there has been a paucity of studies investigating immune-stimulatory agents or cellular therapies in WM. Checkpoint inhibitors currently have a limited role in the treatment of hematologic malignancies, except for a few diseases such as Hodgkin lymphoma. A phase II trial is currently underway investigating pembrolizumab combined with rituximab in patients with R/R WM. This study will enroll patients who have had one prior line of therapy but will exclude those that were previously refractory to rituximab [NCT03630042]. Chimeric antigen receptor (CAR) T-cell therapy has revolutionized the treatment landscape for hematologic diseases; however, there are no data in WM.

Several important considerations limiting its investigation in WM include high cost of therapy, safety concerns given potential for severe cytokine release syndrome and/or neurotoxicity, indolent disease course of WM, and availability of a variety of well-tolerated alternative agents. However, there may still be a role for CAR T-cell therapy in WM, as the possibility for long-term remissions after only one dose is an attractive prospect for patients, especially for medically fit and younger patients. Finally, given the strong expression of surface antigens such as CD20 and CD19, bispecific antibodies and antibody-drug conjugates are of considerable interest and warrant further exploration in the future.[62]

Conclusions

Novel agents targeting BTK and BCL2 have shown to be safe and effective in patients with WM. Future studies will focus on developing fixed-duration combinations regimens with these novel agents aimed at increasing durable responses while minimizing toxicity and cost.

Disclosures

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Table 1. Comparison of BTK Inhibitors

Study	Drug	Population	N	MRR (%)	PFS (%)	G3-4 AEs	AF incidence
Treon, 2015 Treon, 2021	Ibrutinib	RR	63	79	54 (5-yr)	16% Neutropenia 11% Thrombocytopenia 3% Pneumonia	13%, 2% G3-4
Dimopoulos, 2017 Trotman, 2021	Ibrutinib	RR	31	77	40 (5-yr)	10% Neutropenia 10% Hypertension 6% Anemia 6% Diarrhea	0%,
Treon, 2018 Ibrutinib, 2021	Ibrutinib	TN	30	87	76 (4-yr)	10% Neutropenia 10% Hypertension 10% Elevated ALT 7% UTI 7% Rash	20% G2
Dimopoulos, 2018 Buske, 2021	Ibrutinib Rituximab	TN, RR	TN: 34 RR: 41	TN: 76 RR: 76	TN: 70 (4-yr) RR: 71 (4-yr)	13% Hypertension 12% AF 11% Anemia 9% Neutropenia 9% Pneumonia	12% G3-4
Owen, 2020	Acalabrutinib	TN, RR	TN: 14 RR: 92	TN: 79 RR: 78	TN: 90 (2-yr) RR: 82 (2-yr)	16% Neutropenia 5% Anemia 5% Pneumonia 5% ALT elevation	5%, 1% G3-4
Tam, 2020	Ibrutinib	TN, RR	TN: 18 RR: 81	TN: 67 RR: 80	TN: 94 (18 m) RR: 82 (18 m)	11% Hypertension 8% Neutropenia 7% Pneumonia 5% Anemia	15%, 4% G3-4
	Zanubrutinib	TN, RR	TN: 19 RR: 83	TN: 74 RR: 78	TN: 78 (18 m) RR: 86 (18 m)	20% Neutropenia 6% Thrombocytopenia 6% Hypertension 5% Anemia	2%, 0% G3-4
Trotman, 2020	Zanubrutinib	TN, RR	TN: 24 RR: 53	TN: 88 RR: 80	TN: 92 (2-yr) RR: 76 (2-yr)	9% Anemia 6% Neutropenia 5% Cellulitis	5%, 1% G3-4
Sekiguchi, 2020	Tirabrutinib	TN, RR	TN: 18 RR: 9	TN: 89 RR: 89	TN: 94 (2-yr) RR: 89 (2-yr)	11% Neutropenia 7% Rash	0%
Zhou, 2021	Orelabrutinib	RR	47	79	88 (12 m)	9% Neutropenia	0%

						4% Thrombocytopenia 2% Weight increase	
Mato, 2021	Pirtobrutinib	RR	26	68***	NR	10% Neutropenia # 4% Anemia #	1% #

BTK, Bruton Tyrosine Kinase; MRR, major response rate; PFS, progression-free survival; AE, adverse events; AF, atrial fibrillation; TN, treatment-naïve; Yr, year; ALT, alanine aminotransferase; UTI, urinary tract infection; G, grade; R/R, relapsed/refractory; M, months; NR, not reported; ***ORR (MRR not reported); #total study population that includes other B-cell malignancies

Table 2. Selected trials of novel agents in WM (non-BTKi)

Target/Drug Class	Study	Agent (s)	Population	N	MRR (%)	Study Outcome
Proteasome inhibitors						
	Treon, 2014	Carfilzomib Rituximab Dexamethasone	TN, RR	TN: 28 RR: 3	68	NCCN- recommended regimen, primary therapy
	Castillo, 2018 Castillo, 2020	Ixazomib Rituximab Dexamethasone	TN	26	77	NCCN- recommended regimen, primary therapy
	Kersten, 2021	Ixazomib Rituximab Dexamethasone	RR	59	61	
Immunomodulators						
	Treon, 2008	Thalidomide Rituximab	TN, RR	25	64	Dose-limiting neurotoxicity
	Treon, 2009	Lenalidomide Rituximab	TN, RR	16	25	Dose-limiting anemia, low response rate
	Fouquet, 2015	Lenalidomide	RR	17	6	
PI3K inhibitors						
	Castillo, 2017	Idelalisib	RR	5	0	Dose-limiting hepatotoxicity, low response rate
	Tomowiak, 2021	Idelalisib Obinutuzumab	RR	49	65	
	Matasar, 2021	Copanlisib Rituximab	RR	22	NR	No statistically significant improvement in PFS
BCL2 antagonists						
	Castillo, 2021	Venetoclax	RR	32	81	NCCN-recommended regimen, previously treated
CXCR4-targeting agents						
	Treon, 2021	Mavorixafor Ibrutinib	TN RR	10	40	Investigation ongoing
	Treon, 2021	Ulocuplomab Ibrutinib	TN RR	13	100	Drug development stopped per sponsor
Anti-CD20 monoclonal antibodies						
	Furman, 2017	Ofatumumab	TN RR	37	41	NCCN-recommended regimen, previously treated in rituximab-intolerant individuals
Anti-CD38 monoclonal antibodies						

	Castillo, 2020	Daratumumab	RR	13	15	Low response rate

WM, Waldenström macroglobulinemia; BTKi, Bruton tyrosine kinase inhibitor; N, number; MRR, major response rate; TN, treatment-naïve; R/R, relapsed/refractory; NCCN, National Comprehensive Cancer Network; NR, not reported; PFS, progression-free survival

Table 3. Selected ongoing clinical trials in patients with WM

Clinicaltrials.gov ID	Agents	Phase	Eligibility
NCT03620903	Ibrutinib, Bortezomib, Rituximab	II	TN
NCT04263480	Ibrutinib, Carfilzomib vs. Ibrutinib	III	R/R
NCT04260217	APG-2575 (BCL2 inhibitor), Ibrutinib or Rituximab	Ib/II	Arm A: prior ibrutinib Arm B: TN Arm C: 1 prior line
NCT04061512	Ibrutinib, Rituximab vs. DRC	III	TN
NCT03679624	Ibrutinib, Daratumumab	II	TN, R/R
NCT04273139	Ibrutinib, Venetoclax	II	TN
NCT04840602	Ibrutinib, Venetoclax, Rituximab vs. Ibrutinib, Rituximab	II randomized	TN
NCT04624906	Acalabrutinib, Bendamustine, Rituximab	II	TN
NCT04463953	Zanubrutinib, Ixazomib, Dexamethasone	II	TN
NCT05099471	Venetoclax, Rituximab vs DRC	II randomized	TN
NCT04115059	Dasatinib	I	R/R, prior Ibrutinib
NCT02952508	CLR-131	II	R/R
NCT03630042	Pembrolizumab, Rituximab	II	R/R

WM, Waldenström macroglobulinemia; TN, treatment-naïve, R/R, relapsed or refractory; DRC, dexamethasone, rituximab and cyclophosphamide.