Waldenstrom's Macroglobulinemia

A Guide to Treatment Options:

Targeted Therapies:
B-Cell Signaling Pathways

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Introduction

Waldenstrom's macroglobulinemia (WM) is a lymphoma, or cancer of the lymphatic system. WM develops in a type of white blood cell called a B-lymphocyte or B-cell. B-lymphocytes typically develop into plasma cells whose job it is to manufacture immunoglobulins (antibodies) to help the body fight infection. In WM, there is a malignant change during the later stages of B-cell maturation that results in the development of a clone of cells. This clone primarily resides in the bone marrow but is often also present in the lymph nodes and spleen. These clonal cells overproduce an antibody of a specific class called IgM.

Under the microscope, the malignant cells in WM have characteristics of both B-lymphocytes and plasma cells and are called lymphoplasmacytic cells. For that reason, WM is classified as a type of non-Hodgkin's lymphoma called lymphoplasmacytic lymphoma (LPL). About 95% of LPL cases are WM. The remaining 5% do not secrete IgM and consequently are not classified as WM, but often have a similar disease course and are managed in much the same way as WM. WM is a very rare disease – only about 1,500 patients are diagnosed with WM each year in the US. WM is usually indolent (slow growing) and can be managed as a chronic disease for a number of years. Unfortunately, with our currently available therapies it is not yet curable.

As a result of proliferation in the bone marrow, the lymphoplasmacytic cells of WM may interfere with normal blood cell production as the WM cells "crowd out" the healthy blood cells. This may lead to a reduction in normal blood counts. Additionally, in the lymph nodes and other organs, the WM cells may lead to lymph node enlargement or may prevent normal function of other organs.

The over-production of IgM may also cause many of the symptoms associated with the disease. IgM is a large antibody that, unlike other types of antibodies, can bind together and form a pentamer (a group of five IgM antibodies bound together). This pentamer can make the blood thicker than normal, a condition called hyperviscosity. Additionally, sometimes the IgM may incorrectly recognize the body's tissues as "foreign" and attach to them, causing inflammation and injury. For example, in some patients the IgM may bind to nerves and cause damage (peripheral neuropathy) or bind to red blood cells and cause red blood cell destruction in cold temperatures (cold agglutinin).

Although a cure for WM remains elusive, continuing research has resulted in multiple treatment options available to the WM patient, and careful evaluation of all options in formal consultation with one or more knowledgeable physicians is essential before any treatment is undertaken. Treatment recommendations need to be tailored to the individual patient, depending on the characteristics of his or her disease, as well as the patient's baseline medical health issues.

This Treatment Options Guide is not intended to recommend any specific protocol. Such decisions must be made with your physician and with knowledge of current treatment recommendations. Its primary purpose is to provide you with some of the information necessary to discuss treatment options intelligently with your physician and to make these difficult choices more easily.

Unlike many cancers for which early detection and treatment are important to one's survival, WM often, although not always, offers the luxury of time; time to seek out competent physicians and time for a second opinion, which is always considered a good idea when one is unclear or undecided regarding a future course of action. A directory of physicians from around the world who are experts in WM is maintained on the IWMF website at Directory of WM Physicians.

Approach to Treatment

The goal of treatment for WM is to provide disease control and thereby improve quality and duration of life. This Guide and others in our Treatment Options series focus on drug therapies that are used for disease control. There is no single standard of therapy to treat WM; instead, there are many options available to WM patients, including the following:

- **Chemotherapy** with alkylating agents, such as cyclophosphamide and bendamustine, or with nucleoside analogs, such as fludarabine and cladribine;
- **Biologic therapy** with monoclonal antibodies such as rituximab and ofatumumab;
- **Proteasome inhibitors** such as bortezomib, carfilzomib, and ixazomib;
- **Targeted therapies** to the B-cell signaling pathways, including BTK inhibitors such as ibrutinib and zanubrutinib.

Newer targeted therapies being tested (including the BCL-2 inhibitor venetoclax and the second generation BTK inhibitors acalabrutinib, pirtobrutinib, and tirabrutinib) and combinations of these drugs with older therapies are being added to the treatment arsenal.

Some of these drugs may be used as single agents (monotherapy); however, combinations of drugs are frequently used, and many lead to improved overall responses to therapy, either for initial (also called first-line, induction, or primary) treatment or for therapy after previously treated (relapsed) WM.

Treatment is typically required when patients with WM become symptomatic and should not be initiated based on blood test results alone. This applies not only to consideration of first-line treatment but also to treatment for relapsed WM. Initiating treatment early in the course of the disease in most asymptomatic patients does not prolong survival and may result in a range of unpleasant or even serious side effects. Some patients may remain stable and continue to be asymptomatic for years without treatment.

The following symptoms and conditions are considered appropriate reasons to begin treatment:

- Hyperviscosity syndrome (symptoms related to excessive thickness of the blood due to high IgM).
- Anemia (low red blood cell count and low hemoglobin) due to infiltration of the bone marrow with WM cells or destruction of red blood cells due to the abnormal IgM. Anemia is the most frequent condition that leads to treatment for WM. Generally speaking, a hemoglobin level less than 10 g/dL may be used as an indication to begin therapy.
- Thrombocytopenia (platelet count less than <100,000) due to bone marrow infiltration.
- Constitutional symptoms – weakness, fatigue, night sweats, fever, or weight loss.
- Systemic light-chain (AL) amyloidosis, symptomatic cryoglobulinemia, cold agglutinin disease, or moderate to severe peripheral neuropathy. (Explanations about these conditions can be found on the IWMF website in the Symptoms of WM section.)
- Bing-Neel syndrome (infiltration of WM cells into the brain, lining around the brain and/or spinal cord, or fluid surrounding the spinal cord and brain).
- Progressive, symptomatic enlargement of the lymph nodes, liver, or spleen.
- Kidney disease (nephropathy) related to WM.
- Masses of WM cells outside the bone marrow or pleural effusions (fluid in the chest) – treatment is initiated based on the location, size, and rate of cell growth.

Given that WM remains a very heterogeneous disease and no two patients are alike, patients and clinicians must decide which treatment to use based on the individual patient's situation and disease characteristics. These may include the presence of one or more cytopenias (decreased production of blood cells); the need for rapid control of aggressive disease; age; co-morbidities (other chronic health conditions); overall health status; and candidacy for a possible autologous stem cell transplant.

When immediate IgM reduction is required (such as for hyperviscosity syndrome, symptomatic cryoglobulinemia, severe hemolysis due to cold agglutinin disease, etc.), the most rapidly acting therapy is plasmapheresis, which is a procedure to withdraw plasma containing excess IgM from the blood. After plasmapheresis, IgM levels can be reduced significantly, but the effect is only transient, and systemic drug therapy is required for disease control. In some cases, a surgical procedure may be needed to place a central catheter for plasmapheresis. More information about plasmapheresis can be found in a separate Fact Sheet on the IWMF website at IWMF & Affiliate Publications.

Drug treatment can usually be administered in an outpatient setting or at home. The treatment may be given orally, by intramuscular or subcutaneous injection, or by intravenous therapy depending on the specific therapy chosen. Some treatments require that certain medications be taken the day before or the day of treatment in order to minimize associated side effects. Traditionally, treatment may take months to complete, depending on the course of therapy chosen. Newer targeted therapies such as ibrutinib are oral and require regular daily dosing until relapse or significant toxicities develop.

Outside of clinical trials, the choice of therapy after relapse is dependent on first-line therapy use, the quality and duration of response achieved during that therapy, and other variables such as age, tolerance of initial therapy, candidacy for stem cell transplant, etc. Reuse of a first-line single agent therapy or combination is reasonable if a patient achieved a durable or long lasting response; for patients who had short responses or resistance to first-line therapy, relapse therapy may consist of agents of a different class, either alone or in combination with other drugs.

At the biennial International Workshops on Waldenstrom's Macroglobulinemia (IWWM), a consensus panel of international WM experts is appointed to update recommendations for both first-line and salvage therapy in WM patients. These recommendations are developed after extensive review of published and ongoing clinical trials in WM. A similar set of clinical practice guidelines for treatment of WM/LPL is updated regularly by the National Comprehensive Cancer Network (NCCN®), a not-for-profit alliance of the leading US cancer centers. The recommendations discussed in this Treatment Guide are based on both sets of guidelines.

The following is a review of the **targeted therapies known to affect B-cell signaling pathways**. The other drug treatment options listed above are discussed in a series of Treatment Options Guides available on the IWMF website at IWMF & Affiliate Publications.

Targeted therapies: B-cell signaling pathways

To live and multiply, B-cells rely on a very complex series of molecular signals via proteins on their surfaces that in turn initiate a series of reactions inside the cells to enable the cells to carry out their normal functions. This signaling cascade is an essential requirement for the survival of malignant B-cells, and in many cases, several of these signals are enhanced, suppressed, or turned on and off by malignant B-cells so that they can survive and grow. As researchers have revealed more about genes and their protein expression in WM, they are beginning to understand the complicated pathways involved in the disease and develop treatments that target specific portions of these pathways, thereby interfering with survival and growth of WM cells. They are also

discovering that responses to certain targeted treatments may depend upon the cells' genetic makeup, for example, the presence or absence of mutations in the genes MYD88 and CXCR4 in WM cells.

Targeted treatments are different from traditional therapies in several ways, and these differences have important implications for patients. Targeted therapies are more specific for tumor cells than chemotherapy. Almost all the targeted therapies directed to B-cell signaling pathways are daily oral medications, which means that they can be taken at home. This makes them more convenient, but it also means that patients must be diligent about when and how they take their medication. These treatments do not damage stem cells in the bone marrow, although they can have side effects that may require dose reduction or treatment discontinuation. These treatments can result in dramatic improvements in disease status, but they appear to slow or arrest tumor cell growth rather than completely eliminate the cancer. This means that once patients begin these treatments, they may need to continue until the treatments no longer work or until the side effects become intolerable. This represents a significant change from the older therapies that, while not completely eliminating the cancer, are typically administered cyclically for a finite period of time and then discontinued if a patient achieves a response that significantly reduces the disease burden.

Although these targeted agents are currently being administered clinically for WM as single-agent therapies, researchers are investigating whether targeted agents can be used in combination with each other or with other therapies. It may be that combinations can clean out the bone marrow better. If so, combinations may permit patients to go off treatment for extended periods of time, rather than taking targeted agents indefinitely.

The oral targeted agents are very expensive, and not all insurers pay for them. They are not available in all countries. US federal and state regulations are being changed so that Medicare, Medicaid, and private insurers may eventually be required to cover their cost to the same extent that they cover intravenous and injectable drugs, but for now availability and cost remain ongoing issues for many cancer patients in the US and internationally.

BTK inhibitor Ibrutinib (Imbruvica)

Ibrutinib is an inhibitor of an enzyme in the B-cell signaling pathway called Bruton tyrosine kinase (BTK). There was a strong rationale to begin testing this drug in WM patients because BTK is excessively activated by MYD88 L265P, a gene mutation found in approximately 90-95% of WM patients. Activated BTK enhances the survival of WM cells by subsequent activation of an important protein called NF kappa-B in the B-cells. Ibrutinib was approved for WM in 2015 by the US Food and Drug Administration (FDA) and at that time became the first drug to receive FDA approval for the treatment of WM. It has subsequently been approved by Health Canada and by the European Medicines Agency.

Ibrutinib alone, as well as the combination of ibrutinib with rituximab, are included in the NCCN® Guidelines as a Category 1 (preferred regimen) for the treatment of both first-line and relapsed/refractory WM. The standard dose of ibrutinib for WM patients is 420 mg per day.

The clinical trial that led to ibrutinib approval was a Phase 2 study of the drug in 63 symptomatic WM patients who had received at least one prior treatment. The median time to response was four weeks. The overall response rate was 90.5%, with a major response rate of 73%. Treatment-related side effects of grade 2 (moderate) or higher included neutropenia (low neutrophil count) (22%), thrombocytopenia (14%), post-procedural bleeding (3%), nosebleeds associated with the use of fish-oil supplements (3%), and atrial fibrillation associated with a history of arrhythmia (5%). Similar results were observed in other studies. An update to this study after median long-term follow-up of almost 47 months reported overall and major response rates of 90.5% and 79.4%, respectively. No complete responses were observed, but 30.2% achieved a very good partial response

Another Phase 2 study evaluated ibrutinib in 30 symptomatic WM patients who had not been previously treated. The overall response rate was 100%, and the major response rate was 83%. Side effects reported in this study included arthralgias (joint pain), bruising, neutropenia, upper respiratory tract infections, urinary tract infections, atrial fibrillation, and hypertension (high blood pressure).

Overall, treatment with ibrutinib is well tolerated in WM patients. Patients have reported skin rashes and skin and nail changes. New or worsening hypertension (high blood pressure) has been observed. An effect on platelet aggregation, resulting in bleeding complications, has been described. The use of ibrutinib in patients requiring anticoagulants or medicinal products that inhibit platelet function may increase the risk of bleeding, and care should be taken if anticoagulant therapy is used. Acquired von Willebrand disease is a bleeding disorder that may occur with a high IgM level. It is recommended that testing for von Willebrand activity in WM patients with a history of bleeding be considered before starting ibrutinib. In some cases, dose reduction of ibrutinib may help to alleviate some of its side effects.

In a series of 112 WM patients on ibrutinib, the cumulative risk of atrial fibrillation at one, two, and three years was 5.4%, 7.1%, and 8.9%, respectively. Patients with a prior history of atrial fibrillation had a shorter time to recurrence compared to those without such a history. Nearly all patients who developed atrial fibrillation were able to continue ibrutinib following cardiac intervention and/or ibrutinib dose reduction. In patients with pre-existing conditions requiring anticoagulant therapy, alternative treatment options can be considered, although anticoagulation is not a contraindication to the use of ibrutinib. Patients should be monitored closely for bleeding and direct oral anticoagulants, such as apixaban and rivaroxaban, are preferred over warfarin in patients requiring anticoagulation.

Both MYD88 and CXCR4 mutations can impact overall and major responses to ibrutinib. WM patients who have wild-type (unmutated) MYD88 have a lower overall response rate and an absence of major responses, compared to patients with a MYD88 mutation. WM patients with CXCR4 mutations, especially with those termed “nonsense” CXCR4 mutations, have a lower overall response rate and fewer major responses to ibrutinib, as well as delayed responses, than do patients without CXCR4 mutations. “Nonsense” mutations involve a change in the DNA genetic code that introduces a “stop” signal. When new CXCR4 proteins are made, the protein is truncated, resulting in an incomplete protein. The part of the protein that follows a “nonsense” mutation is missing altogether. This differs from a “frameshift” mutation, which is due to a genetic mutation that causes an alteration in the way that the DNA is read. It is recommended (by NCCN® and IWWM) that testing of bone marrow for the MYD88 L265P mutation by AS-PCR (allele specific polymerase chain reaction) or other specialized PCR techniques should be an essential part of the workup of newly diagnosed patients and that patients with an unknown MYD88 and CXCR4 mutation status should be tested for both prior to ibrutinib therapy, as the status of the MYD88 and CXCR4 mutations can affect disease response.

Ibrutinib should not be discontinued, except temporarily for surgical and invasive dental procedures, unless unacceptable toxicity or disease progression occurs. Increase in serum IgM and reduction in hemoglobin can occur if ibrutinib is temporarily withheld and should not necessarily be regarded as treatment failure. Patients may experience withdrawal symptoms such as fatigue, fever, or night sweats, which can be managed with oral prednisone (10 mg twice daily) during the period of time that ibrutinib is withheld. The current recommendations for withholding ibrutinib for surgical procedures depend upon the invasiveness of the procedure and typically vary from 3-5 days before and after.

In patients who discontinue ibrutinib because of disease progression or unacceptable toxicity, 50% have an IgM rebound within the first four weeks afterward. It is suggested that subsequent treatment needed because of disease progression should be started promptly, and consideration should be given to bridging therapy using ibrutinib in combination with the next line of treatment for one or two cycles before completely stopping ibrutinib.

The combination of ibrutinib with the monoclonal antibody rituximab (Rituxan) was approved for WM by the US Food and Drug Administration and the European Medicines Agency in 2018. Approval was based on the Phase 3 iNNOVATE clinical trial, in which the combination of ibrutinib and rituximab was associated with faster time of response, higher rates of response, and improved progression-free survival than placebo and rituximab. However, the absence of a study arm of ibrutinib with placebo has led to a continuing debate on the merits of single-agent ibrutinib vs this combination.

Ibrutinib has been shown to penetrate the central nervous system (brain and spinal cord). Studies have suggested that ibrutinib is effective in the treatment of WM patients with the rare neurological complication of Bing-Neel syndrome (BNS), in which the lymphoplasmacytic cells of WM cells invade the central nervous system. A retrospective study evaluated ibrutinib in 28 patients with BNS; approximately half of the patients took ibrutinib at 560 mg daily and approximately half took the standard dose at 420 mg. Symptomatic improvements were seen in 85% of patients taking 560 mg daily within three months of starting treatment. The 2-year event free survival (survival without additional symptom development related to disease progression) was 80%.

Resistance to ibrutinib has been described in WM patients, especially after several years of treatment. One mechanism of resistance is mutation of the BTK gene, resulting in one altered amino acid in the BTK protein. This is called the C481S mutation, in which a cysteine at position 481 is changed to serine. Other causes of ibrutinib resistance are under investigation.

Many of the side effects of ibrutinib occur because it not only inhibits BTK, the desired target, but also non-specifically inhibits a number of other similar cellular proteins (called kinases). These so-called off-target effects can cause some of the adverse effects seen with ibrutinib. Newer, more specific BTK inhibitors have been and are being developed to improve responses, reduce some of the side effects seen with ibrutinib, and overcome resistance.

BTK inhibitor Acalabrutinib (Calquence)

Acalabrutinib, a second generation BTK inhibitor, was designed to reduce side effects by more specifically inhibiting BTK while minimizing inhibition of other kinases. This targeted therapy was evaluated in a Phase 2 study of 106 WM patients, of whom 14 were treatment naïve and 92 previously treated. At a median follow-up of 27 months, acalabrutinib was associated with an overall response rate of 93% in both groups of patients, with a major response rate of 79% in treatment naïve and 80% in previously treated patients. Common adverse events included headache, diarrhea, bruising, fatigue, nausea, and muscle aches. The most serious adverse events of grade 3 or worse included neutropenia and lower respiratory tract infections. The proportion of patients who had atrial fibrillation was 5%. Typical dosing for WM patients is 100 mg twice daily.

Acalabrutinib is approved for the treatment of chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), and mantle cell lymphoma. It is not approved for WM, but it can be prescribed off-label. Although it is not a preferred regimen in the NCCN® Guidelines, it is listed as one of the other recommended regimens for previously treated WM patients. Acalabrutinib, like ibrutinib, relies on binding to the amino acid cysteine in position 481 of BTK. So, if resistance to ibrutinib is based on the BTK C481S mutation, there also will likely be resistance to acalabrutinib.

BTK inhibitor Zanubrutinib (Brukinsa)

Zanubrutinib, another second generation BTK inhibitor, was also designed to reduce side effects by more

selectively inhibiting BTK while minimizing inhibition of other kinases.

A Phase 1/2 clinical trial looked at zanubrutinib in 77 WM patients, including 24 who were treatment naïve and 53 who were previously treated. At a median follow-up of 36 months, zanubrutinib showed an overall response rate of 96%, with a major response rate of 82%. Adverse events of minor bruising or bleeding and a rate of 5% atrial fibrillation were observed.

A more recent Phase 3 study compared zanubrutinib to ibrutinib in symptomatic WM patients. Although a very good partial response was attained in patients on zanubrutinib (28%) vs patients on ibrutinib (19%), that result was not statistically significant. Zanubrutinib was associated with a lower rate of atrial fibrillation than ibrutinib (2% vs 15%). Multiple other side effects, such as muscle spasms, contusions, diarrhea, peripheral edema (leg swelling), and pneumonia were seen in fewer patients on zanubrutinib compared to ibrutinib. On the other hand, there was a higher rate of neutropenia (low neutrophil counts in the blood) with zanubrutinib than ibrutinib (29% vs 13%), but an increase in infections, which might be expected when there is neutropenia, was not seen. A separate arm of this study evaluated WM patients without the MYD88 L265P mutation and found that zanubrutinib was able to induce responses in these patients, with an overall response rate of 77%.

Zanubrutinib dosing in WM is 160 mg twice daily. At the time of this Treatment Options Guide update, November 2021, zanubrutinib has approval in the treatment of WM patients by the US Food and Drug Administration, Health Canada, Australia, and has conditional approval from China National Medical Products Administration (NMPA) for the treatment of relapsed or refractory WM. The European Medicines Agency approved zanubrutinib for the treatment of patients with WM who have received at least one prior therapy or for the first-line treatment of patients unsuitable for chem-immunotherapy. Zanubrutinib has been added to the National Comprehensive Cancer Network (NCCN®) guidelines as a Category 1 (preferred) treatment for patients that are previously untreated and those with relapsed disease.

Zanubrutinib, like acalabrutinib and ibrutinib, also relies on cysteine at position 481 of BTK. So, if resistance to ibrutinib is based on the BTK C481S mutation, there will be resistance to zanubrutinib as well.

Other BTK inhibitors

Several other BTK inhibitors are in development. Tirabrutinib (Velexbru) was evaluated at a dose of 480 mg once daily in 27 WM patients, both treatment naïve and previously treated. The overall response rate was 94% and the major response rate was 78% in treatment naïve patients, whereas the overall response rate was 100% and the major response rate was 89% in previously treated patients. Rash was reported in 41% of patients, and serious neutropenia was reported in 7%.

Because mutations in BTK can be acquired by patients on ibrutinib and lead to treatment resistance, third generation BTK inhibitors that bind differently to BTK are now being evaluated. These include ARQ 531 and pirtobrutinib (LOXO-305), both are which are in clinical trials with WM patients whose disease has progressed while on ibrutinib.

BCL-2 inhibitor Venetoclax (Venclexta or Venclyxta)

Venetoclax is an inhibitor of BCL-2 (B-cell lymphoma 2), a member of the BH3 family of proteins that regulate cell death (apoptosis). BCL-2 inhibits normal apoptosis, resulting in cells that live longer. If cancer cells over-express BCL-2, extended survival of the cancer cells causes the population of cancer cells to expand. Venetoclax has been approved in the US for the treatment of CLL and SLL. Venetoclax has been studied in a Phase 2 trial

of relapsed/refractory WM, where it has shown promising interim results, with an overall response rate of 90% and a major response rate of 83%. Grade 3 or worse adverse events have included neutropenia, anemia, and diarrhea.

Venetoclax dosing is somewhat unusual, in that at the beginning of treatment, it must be ramped up from a low dose to a higher dose over a period of several weeks in order to avoid an adverse event called tumor lysis syndrome. Tumor lysis syndrome (TLS) is a condition that occurs when a large number of cancer cells die quickly. The dying cells release large amounts of potassium, phosphate, and uric acid into the blood, which can cause heart or kidney problems, lead to kidney failure, and become life-threatening. In the Phase 2 trial of WM patients, only one TLS event was reported, and that was based on laboratory evidence of the condition; no clinical symptoms of TLS occurred. To help prevent TLS, it is recommended that patients be treated prophylactically with the drug allopurinol and maintain good hydration during venetoclax ramp-up dosing. Dosing after ramp-up in this trial was 800 mg once daily.

Based on promising results seen with the combination of ibrutinib and venetoclax in CLL patients, a Phase 2 study using this combination in treatment naive WM patients with the MYD88 mutation has begun. Both drugs are being administered over two years, with four years of follow-up. The hoped-for outcome is that this combination will eliminate the majority of malignant cells in the bone marrow and result in a treatment response that may allow patients to have a prolonged treatment break.

Second generation BCL-2 inhibitors are now in development, as well as other medications that target additional BH3 proteins.

PI3K/AKT/mTOR pathway inhibitor everolimus (Afinitor)

Everolimus blocks mTOR, a protein in the PI3K/AKT/mTOR pathway that promotes cell growth and survival. This pathway is present in several cell types, including B-cells, and is therefore used to treat solid cancers as well as B-cell cancers. The effectiveness of PI3K inhibition in B-cell cancers appears to result from interference with the ability of the cancer cells to respond to signaling in the tumor microenvironment.

A Phase 2 trial of everolimus in 60 relapsed/refractory WM patients reported a partial response rate of 50% and a major response rate of 23%. Toxicities included grade 3-4 (severe) anemia (27%), leukopenia (22%) thrombocytopenia (20%), diarrhea (5%), fatigue (8%), and pneumonitis (5%). Among previously untreated, symptomatic WM patients, the overall and major response rates were 72% and 60%, respectively. A discordance (lack of agreement) between serum IgM levels and bone marrow response was common and made response assessment difficult. Mouth sores frequently occurred (8%), and an oral dexamethasone swish and spit solution was helpful.

Everolimus is recommended as an option for therapy in relapsed/refractory WM, although owing to the toxicities associated with it (see above), everolimus is best considered in patients who are unresponsive to, or have progressed after, multiple lines of other, better-tolerated therapies. Serial bone marrow biopsies may help to clarify the disease response to everolimus. The drug is currently accessible in the US as an off-label indication for WM; however, it is not available for WM in many other countries.

Other PI3K/AKT/mTOR pathway inhibitors

Within the PI3K/AKT/mTOR pathway there are components other than mTOR that can be targeted to reduce the growth and survival of cancer cells.

One of the earlier inhibitors developed in this pathway was idelalisib (Zydelig), which is targeted to the enzyme PI3K kinase. Idelalisib is FDA-approved for CLL, relapsed follicular lymphoma, and relapsed SLL. It was evaluated in a Phase 1/2 study in ten previously treated WM patients and was associated with an 80% overall response rate. The most common grade 3 or greater adverse events included neutropenia, diarrhea, and liver toxicity. Another Phase 2 study of 30 previously treated WM patients was terminated early due to liver toxicity.

Newer PI3K inhibitors have been developed to reduce the toxicities associated with idelalisib. They include copanlisib (Aliqopa), duvelisib (Copiktra), and umbralisib (Ukoniq). These newer inhibitors have been FDA-approved for CLL and/or several non-Hodgkin's lymphomas and have been studied in WM with encouraging results; however, none are currently included in the NCCN® Guidelines or the IWWM consensus panel recommendations for WM patients.

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About the IWMF

The International Waldenstrom's Macroglobulinemia Foundation (IWMF) is a patient-founded and volunteer-led, nonprofit 501(c)(3) organization with an important vision, "A World Without WM," and a mission to "Support and educate everyone affected by WM while advancing the search for a cure."

More information about Waldenstrom's macroglobulinemia and the services and support offered by the IWMF and its affiliate organizations can be found on our website, www.iwmf.com.

The IWMF relies on donations to continue its mission, and we welcome your support. The Foundation maintains a Business Office at 6144 Clark Center Ave., Sarasota, FL 34238. The Office can be contacted by phone at 941-927-4963, by fax at 941-927-4467, or by email at info@iwmf.com.

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