used. Acquired von Willebrand disease is a bleeding disorder and 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 a series of 112 WM patients on ibrutinib, the cumulative risk of atrial fibrillation at 1, 2, and 3 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 atrial fibrillation requiring anticoagulant therapy, alternative treatment options to ibrutinib should be considered.

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 an MYD88 mutation. WM patients with CXCR4 mutations have a lower overall response rate and fewer major responses, as well as delayed responses, than do patients without CXCR4 mutations. It is recommended that testing of bone marrow for the MYD88 L265P mutation by AS-PCR (allele specific polymerase chain reaction) 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.

Ibrutinib should not be discontinued, except temporarily for surgical procedures, unless 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. The current ibrutinib-hold recommendations for surgical procedures are: one-week hold for major surgery, three-day hold for minor surgery, and no hold for procedures like cataract surgery, minor dental work, and colonoscopy without biopsy.

The combination of ibrutinib with the monoclonal antibody rituximab (Rituxan) was approved for WM by the US Food and Drug Administration in 2018. Ibrutinib alone and the combination of ibrutinib and rituximab are included in the NCCN® Guidelines list of preferred regimens for the treatment of relapsed/refractory WM; they are not considered preferred regimens for first-line therapy but can be used as alternate options.

Resistance to ibrutinib has been described in WM patients and remains under investigation. Newer generation BTK inhibitors are in development to improve responses, reduce some of the side effects with ibrutinib, and overcome resistance. Acalabrutinib (Calquence), which has been approved for relapsed/refractory mantle cell lymphoma, and zanubrutinib are both further along in development than others and are in clinical trials of WM patients. Neither has yet been approved by the FDA for WM.

**Venetoclax (Venclexta or Venclyxta) – BCL2 inhibitor**

Venetoclax is an inhibitor of BCL2, which is a member of the BCL2 family of proteins that regulate cell death (apoptosis). It has been approved in the US for the treatment of chronic lymphocytic lymphoma (CLL) and small lymphocytic lymphoma (SLL) in patients who have received at least one prior therapy. Venetoclax is currently in a Phase II trial of relapsed/refractory WM, where it is showing early promising results.

**Everolimus (Afinitor) – mTOR inhibitor**

Everolimus blocks mTOR, a protein in the PI3K/AKT pathway that promotes cell growth and survival. Used to treat advanced kidney cancer as well as advanced breast cancer, among others, everolimus may also stop tumors from developing new blood vessels, which helps to limit their growth.

A Phase II trial of everolimus in 60 relapsed/refractory WM patients reported a partial response rate of 50% and a major response rate of 23%. The median time to response was 2 months, and the median progression-free survival was 21 months. Toxicity was hematologic, with grade 3-4 (severe) anemia at 27% and thrombocytopenia at 20%. Pulmonary toxicity such as pneumonitis was also reported. 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 were common and made response assessment difficult. Mouth sores frequently occurred, and an oral dexamethasone swish and spit solution was helpful.

A Phase I/II study of everolimus in combination with rituximab, and with or without bortezomib, in 46 WM patients reported an overall response rate of 89% and a median progression-free survival of 21 months in the 36 patients who received full dose therapy.
Everolimus is currently recommended as an option for salvage therapy in WM, although owing to the toxicities associated with it, everolimus may be best considered in patients who are unresponsive 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 targeted therapies/pathway inhibitors in development**

There are several other pathway inhibitors in pre-clinical development and in clinical trials for B-cell non-Hodgkin's lymphoma and chronic lymphocytic leukemia, and some are being assessed specifically for WM as well. It remains to be seen how safe and effective they will prove to be and whether they will receive FDA approval or off-label indication for WM treatment. These include duvelisib (PI3K inhibitor), umbralisib (PI3K inhibitor), copanlisib (PI3K inhibitor), GS-4059 (BTK inhibitor), fostamatinib (SYK inhibitor), entospletinib (SYK inhibitor), and cerdulatinib (SYK, JAK1, JAK3, and TYK2 inhibitor), among others.

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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 mission: to offer mutual support and encouragement to the Waldenstrom's macroglobulinemia community and others with an interest in the disease; to provide information and educational programs that address patients' concerns; and to promote and support research leading to better treatments and ultimately, 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.